Eyelid reconstruction

Urinary bladder matrix offers new xenograft for patients with large, difficult-to-treat lesions

By Lynda Charters; Reviewed by Mark A. Alford, MD, FACS

Xelpros™
(latanoprost ophthalmic emulsion) 0.005%

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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.

Please see Important Safety Information on the back cover and brief summary of Full Prescribing Information inside.
Urinary bladder matrix offers new xenograft for patients with large, difficult-to-treat lesions

By Lynda Charters; Reviewed by Mark A. Alford, MD, FACS

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

XELPROSTM (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
XELPROSTM 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 XELPROSTM is administered. After discontinuation of XELPROSTM, 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
XELPROSTM 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
XELPROSTM 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
XELPROSTM 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
XELPROSTM should be used with caution in patients with a history of herpetic keratitis. XELPROSTM 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 XELPROSTM 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 XELPROSTM, 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 XELPROSTM, 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.
EYELID RECONSTRUCTION

Urinary bladder matrix offers new xenograft for patients with large, difficult-to-treat lesions

By Lynda Charters; Reviewed by Mark A. Alford, MD, FACS

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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Surgery

Eyelid reconstruction

Urinary bladder matrix offers new xenograft for patients with large, difficult-to-treat lesions

By Lynda Charters; Reviewed by Mark A. Alford, MD, FACS

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.

Erinary bladder matrix offers new xenograft for patients with large, difficult-to-treat lesions

By Lynda Charters; Reviewed by Mark A. Alford, MD, FACS

**URINARY BLADDER MATRIX** is a skin substitute material derived from porcine (pig) bladder used extensively in general surgery and to treat burns. The use of this product has now been extended to include periorbital reconstruction and is an effective alternative to granulation, skin grafts, or flaps in selected patients, according to Mark A. Alford, MD, FACS, an oculoplastic surgeon with North Texas Ophthalmic Plastic Surgery, Privia Medical Group, in Fort Worth.

“Our skin’s dermal extracellular matrix is a complex meshwork of proteins and carbohydrates, the main protein being collagen,” he said. “Collagen is supported by glycosaminoglycans and is woven together with proteoglycans and attached to cells with integrin and fibronectin.”

Alford explained these dermal components provide strength and structure to the skin and allow healing to take place.

**HOW IT WORKS**

The product (Cytal Wound Matrix and Micromatrix, Acell Inc) provides a source of naturally occurring growth factors, multiple types of collagen, laminin, fibronectin, proteoglycans, and elastin.

**RECONSTRUCTING THE EYELID**

A. A patient with a serious defect can face issues that impact their quality of life. B. A paste is used to fill the defect. C. A 1-ply sheet is used to cover the defect. It is bolstered for 2 weeks, and antibiotic ointment is applied. (Photos courtesy of Mark A. Alford, MD, FACS)

**THERAPEUTICS**

**STUDY TARGETS OCULAR DAMAGE FROM CHRONIC INTRAVITREAL INJECTIONS**

One adverse event is acute transient increases in IOP

By Lynda Charters; Reviewed by Richard Rosen, MD

**INTRAVITREAL INJECTIONS USED** to treat a variety of ocular diseases may contribute to progressive visual loss with chronic administration over years. One adverse event of intravitreal injections is acute transient increases in IOP that may increase the risk of damage to the macula and optic nerve over the long term.

To underscore the importance of this issue and the numbers of patients at potential risk, Richard Rosen, MD, and colleagues pointed out that more than 6 million intravitreal injections were administered in the United States in 2016. Because these injections have been used for a relatively short period, the definitive consequences of chronic use remain to be determined. A recent study reported that patients who received 7 or more intravitreal injections annually had an increased risk of undergoing glaucoma surgery.1

Rosen is deputy chair for Clinical Affairs, Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, the Belinda Bingham Pierce and Gerald G. Pierce Distinguished Chair of Ophthalmology, and director of Retina Services, New York Eye and Ear Infirmary of Mount Sinai, New York.

This happens, Rosen explained, because the injections cause the IOP to elevate to 3 times the normal level. He noted that the IOPs return to normal within minutes of the injections, but he and his colleagues wanted to determine what the immediate impact is on the ocular blood flow.

“Recently, we have become aware that repeated mild trauma to central nervous system structures, such as minor head bumps in athletes, can lead to degenerative brain injury with devastating results, decades later,” he said. “We wanted to better

Continues on page 14: Injections
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• Provide preservative-free, sustained coverage for up to 30 days²

INDICATION
DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

IMPORTANT SAFETY INFORMATION

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

WARNINGS AND PRECAUTIONS
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during treatment.

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

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

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

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

ADVERSE REACTIONS
The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

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

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

DEXTENZA Package Insert for full prescribing information for DEXTENZA (06/2019)

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

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

5 WARNINGS AND PRECAUTIONS
5.1 Intracocular 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. Intracocular pressure should be monitored during the course of the treatment.

5.2 Bacterial Infection
Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infection. In cases of acute purulent conditions, steroids may mask infection and enhance existing infection [see Contraindications (4)].

5.3 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)].

5.4 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)].

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

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labelling:
- Intracocular 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)]

6.1 Clinical Trials Experience
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 optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation; delayed wound healing; secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera [see Warnings and Precautions (5)].

DEXTENZA was studied in four randomized, vehicle-controlled studies (n = 567). The mean age of the population was 68 years (range 35 to 87 years), 59% were female, and 83% were white. Forty-seven percent had brown iris color and 30% had blue iris color. The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intracocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies with DEXTENZA in pregnant women to establish a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, administration of topical ocular dexamethasone to pregnant mice and rabbits during organogenesis produced embryoidal lethality, cleft palate and multiple visceral malformations [see Animal Data].

Data
Animal Data
Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryoidal lethality and a high incidence of cleft palate in a mouse study. A daily dose of 0.75 mg/day in the mouse was approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis. In a rabbit study, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.36 mg/day on gestational day 6 followed by 0.24 mg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A daily dose of 0.24 mg/day is approximately 6 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis.

8.2 Lactation
Systemically administered corticosteroids appear in human milk and could suppress growth and interfere with endogenous corticosteroid production; however the systemic concentration of dexamethasone following administration of DEXTENZA is low [see Clinical Pharmacology (12.3)]. There is no information regarding the presence of DEXTENZA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production to inform risk of DEXTENZA to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DEXTENZA and any potential adverse effects on the breastfed child from DEXTENZA.

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

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

17 PATIENT COUNSELING INFORMATION
Advises patients to consult their surgeon if pain, redness, or itching develops.

Manufactured for: Ocular Therapeutix, Inc.
Bedford, MA 01730 USA
PP-US-DX-0072-V2

SUMMER IS HERE and with it sunshine and warmer weather. As we continue to practice social distancing and take other precautions in our daily lives, it is the perfect time to catch up on the latest developments in ophthalmology in this issue of Ophthalmology Times.

On our website, the Ophthalmology Times team continues to provide the latest coverage of COVID-19-related issues, including information that can help you navigate the path to reopening your practice.

On the cover, we focus on surgery and the magic of eyelid reconstruction with Mark A. Alford, MD, FACS. He details how the use of urinary bladder matrix, a skin substitute material made from porcine bladder, has been used successfully in periorbital reconstructive procedures. The use of the material, from porcine bladders, has been extended to include periorbital reconstruction and is an alternative to granulation, skin grafts, or flaps in selected patients.

Therapeutics also kicks off our cover content with a study that examines ocular damage from chronic intra-vitreal injections. Richard Rosen, MD, points out that patients who received 7 or more intra-vitreal injections annually had an increased risk of undergoing glaucoma surgery. The study results could pave the way for doctors to pretreat patients with medications to reduce the IOP spikes after receiving injections to prevent possible long-term damage.

Our therapeutics coverage also focuses on a new molecule for allergic conjunctivitis. The FDA recently approved the first prescription-only topical ocular formulation of the second-generation antihistamine cetirizine for the treatment of ocular itching associated with allergic conjunctivitis.

In our special section, we look at IOL trends. Devesh Varma BENG, MD, FRCSc, discusses a new IOL that provides both near and intermediate distance. The Vivity lens from Alcon has been approved by the FDA. Gerald J. Roper, MD, examines some current trends in IOLs and details how advanced technology IOLs may be implanted at an inadequate rate. Imaging developments continue to draw a lot of attention. In this issue, we talk to Atalie C. Thompson, MD, MPH, who discusses research which determined that the segmentation-free DL algorithm performed better than global and sectoral RNFL-thickness parameters for discriminating glaucomatous from control eyes.

Another hotbed of innovation is in clinical diagnosis. An interesting development looks at subthreshold laser therapy, which may reduce intravitreal injections for patients with diabetic macular edema. According to Pauline T. Merrill, MD, given the excellent safety profile of the ST laser, this may be a reasonable treatment approach in such patients, either alone or in combination with a CW focal laser.

We are always impressed with developments we see coming in gene therapy. In this issue, we look at a gene therapy treatment that may hold promise for treating an inherited ocular disease, achromatopsia after a study found it provided some visual improvements in treated patients. According to M. Dominik Fischer, MD, PhD, a study offers clinical proof of concept for viral vector-mediated gene supplementation therapy of inherited day blindness caused by pathogenic variants in the cone photoreceptor-specific gene CNGA3.

The area of device technology continues to see myriad advances. Hari Jayaram, MD, PhD, talks about a minimally invasive gelatin stent that has been found to lower pressure in glaucoma cases. In this issue, we also focus on the eye and COVID-19, dishing up facts, myths, and with it time to delve into the latest issues that clinicians can optimize their practice even in the face of COVID-19.
Therapeutics

1 Study looks at ocular damage from chronic intravitreal injections
Research has found that chronic intravitreal injections may lead to ocular damage.

12 New molecule for allergic conjunctivitis makes debut
First new therapy in nearly a decade offers another option for physicians, patients.

13 The dropless future: SLT as a first-line treatment for glaucoma
Drop tolerance, adherence remain challenges for physicians and patients.

15 Study reviews medication adherence, visual progression
Research seeks benefits and options for open-angle glaucoma patients.

Surgery

10 Examining the results of MIGS device versus trabeculectomy
Review examines safety and effectiveness of implantation in POAG patients.

Imaging

16 Investigators target algorithm for diagnosing glaucoma
Research finds automated segmentation software examines OCT scans.

Clinical Diagnosis

18 SLT laser therapy may reduce DME intravitreal injections
With excellent safety profile, option may be reasonable treatment approach.

Gene Therapy

29 Subretinal gene therapy safe with visual benefit
Study finds use in achromatopsia may revitalize cone photoreceptors.

Device Technology

30 Minimally invasive glaucoma shunt delivers for patients
An option for ophthalmologists, a gelatin stent has been found to lower pressure.

31 Amid pandemic, FDA taking aim at medical products
Administration targets scam artists on internet as pace of research steps up.

A time of change
Coronavirus forces ophthalmology to pivot

By Peter J. McDonnell, MD
director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of Ophthalmology Times®.

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“Change is inevitable. Growth is optional.” —John Maxwell

THANKS TO THE novel coronavirus, a lot of things are changing, and changing quickly. Sometimes the changes are difficult and sometimes they are upsetting. But it seems clear to me that a lot of the changes we have had to make have taught us some valuable lessons and have been net positives. When the virus eventually clears and we return to “normal,” that normal will be better than the old normal in a few ways.

When it comes to education, for example, we have seen how universities like mine have quickly evolved from having a bunch of students in a lecture hall, listening to the professor in the front of the room, to an online format in which lecture material is mastered from wherever the student happens to be.

In my department, this process actually began years ago, with lectures put online and the time that residents spend in class devoted to examining and caring for actual patients with the problems covered in the lectures. This allows faculty to know that the concepts covered in the lecture have actually been absorbed into the brilliant brains of our residents and are able to be applied to the care of patients.

Recently, I had the opportunity to speak to more than 500 ophthalmologists, most of whom live in South America and Europe. This was fun and it seemed the lecture was interesting as evidenced by the very astute questions from the audience. What was particularly nice is that spending time with and learning from international ophthalmologists who may live literally on the other side of the world, and commonly ophthalmologists from many time zones are all part of the department’s Grand Rounds.

It is fun to visit other countries and to enjoy time with and learn from impressive ophthalmologists in their cities, but it has been a bit of a blessing not to spend so much time in airports and otherwise pay the price of having to travel. I find myself hopeful that after this pandemic we will continue to use technology to teach each other without having to travel.

Another change has been the need to empty out our waiting rooms. This has been achieved by using telemedicine whenever possible and also realizing that it is important to have our clinics operate efficiently and no longer think it appropriate to run behind schedule and park patients in filled waiting rooms. Patient satisfaction scores show that Johns Hopkins and Wilmer patients love video visits and not being told to sit in a waiting room someplace. My wish is that physician offices never return to the bad old days of long waits to see the doctor.

On a personal note, the pandemic has allowed me to reliably schedule time for physical fitness. Apparently this is common, and companies that make exercise equipment for the home are experiencing tremendous back orders, unable to meet the demand for their products. This is another trend I hope will survive the pandemic. The downside of this change is that I may eventually end up muscle bound, like those professional body builders, and have difficulty eating sandwiches because my biceps are too large.

Recently, while speaking to a group of ophthalmologists, a joke occurred to me and I inserted it into my talk. After making what I thought was a particularly witty aside, I paused. The response from my audience on Zoom was total silence. In this period of rapid change, it is comforting to know that some things haven’t changed at all.
Indication

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

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see Brief Summary of Prescribing Information on adjacent page.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use

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

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

4 CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation [see Adverse Reactions (6.2)].

6 ADVERSE REACTIONS
The following adverse reactions are described elsewhere in this labeling:

- Hypersensitivity [see Contraindications (4)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

In five clinical studies of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. One hundred-seventy 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 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval 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 [see Contraindications (4)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) 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 [see Clinical Pharmacology (12.3) in the full prescribing information].

Data
Animal Data
Lifitegrast administered daily by IV injection to rats, from pre-mating through gestation Day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing five, 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 fatal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation
Risk Summary
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production.

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 [see Clinical Pharmacology (12.3) in the full prescribing information]. 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Manufactured for:
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NOVEL INTRAOCULAR LENS PROVIDES BOTH NEAR AND INTERMEDIATE DISTANCE

Nondiffrae technology uses a pair of smooth-surface transition elements on IOL

By Louise Gagnon; Reviewed by Devesh Varma, MD, BEng, FRCSC

According to Varma, these elements result in continuous extended range of vision as opposed to separate points of focus.

**STUDY RESULTS**

Varma, who participated as a study investigator in the meeting, noted that both patients and assessors were masked in an international clinical trial, which included participants from the United States, Canada, the UK, Spain, and Australia. The research team aimed to show that the investigational lens is as good as or superior to the AcrySof IQ lens. Patients received either the study lens or the IQ lens in both eyes.

The study lasted 6 months and measured distance-corrected intermediate visual acuity (DCIVA) and best-corrected distance visual acuity (BCDVA). In terms of DCIVA, the EDOF lens proved superior to the IQ lens, with a change of 0.2 log units or better on the logMAR chart in 50% of eyes. The 2 types of lenses performed equally regarding BCDVA.

With respect to defocus, the EDOF lens was 0.5 D more than the monofocal lens at 0.2 logMAR. The investigational lens met expectations in how the 2 IOLs’ defocus curves compare, according to Varma. “There is a pretty continuous range of focus, which is what you want to see,” he said.

Specifically, there was continuous focus from distance to arm’s length, or 1.5 D defocus, he said. Furthermore, the findings showed that the vast majority of patients (94%), without wearing spectacles, reported good or very good vision at distance, and 92% reported good or very good vision at arm’s length.

The study lens offered slightly less contrast sensitivity than the monofocal lens, but the difference was not meaningful.

“Diffractive optics have been around for a long time,” he said. “Just because [a lens] is diffractive, it does not mean it will cause a halo.”

Some camera lenses and telescopes use diffractive optics to correct for chromatic aberrations without producing halos. However, Varma stressed that diffractive designs do not necessarily lead to halos.

“Diffractive optics have been around for a long time,” he said. “Just because [a lens] is diffractive, it does not mean it will cause a halo.”

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Patients who had the Vivity lens implanted reported low levels of halos, glare, and starbursts, comparable to visual disturbances reported among patients who had the monofocal lens.

Varma noted that he believes glare and starbursts may occur with any lens due to other factors such as dry eyes, but halos are more specific adverse effects in presbyopia-correcting lenses. Those are the photic phenomena Varma considers more when evaluating a new lens design, he said.

The Vivity IOL’s nondiffractive design may be part of the reason it does not seem to produce as many halos. However, Varma stressed that diffractive designs do not necessarily lead to halos.

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Some camera lenses and telescopes use diffractive optics to correct for chromatic aberrations without producing halos.

“The comparator in this study, the AcrySof IQ lens, is an above-average performing lens,” Varma concluded. “It [the Vivity lens] was up against a tough standard.”

Dr Varma has no financial disclosures related to this content.
Protecting cataract patients and their surgeons’ practices

Maximizing refractive surgery is key to ensuring prosperous future

By Gerald J. Roper, MD; Special to Ophthalmology Times

As cataract surgeons, we can address our unfavorable medical climate by returning to this basic care tenet: provide the very best care we can offer to patients.

If I were offered cataract surgery and had significant astigmatism, I would only accept an offer to have my astigmatism corrected. I know many cataract surgeons would respond similarly. In the interest of patient function and satisfaction, we have refined astigmatism correction in many patients’ eyeglasses year after year, while we have also had the opportunity to improve those patients’ function by implanting a toric IOL, and providing simultaneous refractive biopics. The time to act is now. The same approach can be applied to presbyopia. Our patients deserve to understand this very high-value proposition.

These predicaments conjure up many questions. Is our own anxiety about delivering outcomes the real reason advanced technology IOLs (AT-IOLs) are implanted at such an inadequate rate? If we see the value in them, why is that not related to patient care we can offer to patients? Regardless of the reasons, we can and must do better. Here is the key.

OUTCOME EXCELLENCE

We can deliver outcome excellence by calculating lenses to within median absolute error of less than 0.25 D. Current optical coherence tomography (OCT) biometry (IOLMaster 700, Carl Zeiss Meditec; Lensstar LS 900, Haag-Streit), performed on a controlled ocular surface, especially when applied in redundant tandem and processed through review and planning software (Holladay IOL Consultant Software and Surgical Outcomes Assessment; Holladay Consulting) with the Barrett Universal II formula, is essential to my practice.

Additionally, intraoperative capsulorhexis and incision control through microscopic computer guidance systems are readily available and beneficial. Implementing a microscopic computer guidance system (Zeiss CALLISTO Eye, Carl Zeiss Meditec) in 2014, along with swept-source OCT biometry and interference, has improved my refractive outcomes. This is in addition to IOL formula improvements before and since then, bringing more than 90% of my patients to within 0.50 D refractive targeting.

LIMIT COMPLICATIONS

Diligence in limiting intraoperative complications in cataract surgery is essential to the long-term ocular health of our patients and our ability to give them maximal refractive correction. All cataract surgeons and partnering industry deserve credit for the rapid development and continuation of significant cataract safety advances.

The spectrum of improvements has been vast, from advances in extraction systems’ pumps and energy delivery, to chamber and iris management, incision and rhexis control, IOL insertion and placement, chopping techniques, and other surgeon-specific skills. By incorporating a lens fragmentation device (miLOOP, Carl Zeiss Meditec) and technique in 2018 I was able to perform safer surgery and, surprisingly, further improve refractive outcomes. In a recent outcomes series in my own practice, patients realized refractive outcomes within 0.25 D of target more than 90% of the time and within 0.50 D in more than 98% of eyes.

The fragmentation device uses centripetal energy, which appears to reduce stress on zonules, resulting in more predictable refractive outcomes. Like all surgical devices, it requires the development of surgical acumen, after which surgeons and patients can realize tangible benefits in reduction of morbidity and improvement in function.

CONCLUSION

We are up to this challenge. We can surgically improve functional vision quality and range and even improve the comorbidities of other chronic ocular conditions. Patients will choose these high-value offerings. Our practices’ health and our satisfaction and integrity will improve as our patients’ ocular function and long-term health improves.

The best, overall long-term outcome is achievable by applying the right technologies during the pre-evaluation phase for testing and planning, as well as by using the right technology in the operating room.

take-home

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‘We can deliver outcome excellence by calculating lenses to within median absolute error of less than 0.25 D.’

—Gerald J. Roper, MD

Patients understand the value and the limitations of our latest and greatest vision technologies. Spoken plainly, patients generally understand that human bodies are asymmetric and heal variably. Pointing out to them that each of their single corneas are also asymmetric and that their eyes, although a pair, are different from each other can help elucidate, for example, that even if one measured estimate of the power of a lens implant in one patient’s eye is the same as it would be for another patient’s eye, with the same measured dimensions, those 2 different people with 2 different eyes may not heal in exactly the same manner and could have different focus outcomes.

This means the same thing to patients as it does to us; distance refractive outcomes are neither perfect nor guaranteed. Patients can then accept that improvement in brightness, contrast, stereopsis, and range represents valuable functional improvement, which would also help them to accept imperfect, yet excellent visual outcomes.

Gerald J. Roper, MD

Dr Roper has been in private practice for more than 30 years at Roper Advanced Eye Care in Batonville, Illinois. He has also participated in cataract medical education through the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgery for more than 30 years and, in cooperation with industry, is a consultant for Carl Zeiss Surgical.
A new study is one of the first head-to-head clinical reviews comparing a minimally invasive glaucoma surgery (MIGS) device with trabeculectomy in patients with primary open-angle glaucoma (POAG). The MicroShunt (Santen) is a subconjunctival glaucoma device made from polystyrene-block-isobutylene-block-styrene (SIBS) material. It is 8.5 mm in length, has a 70-μm lumen, and is highly biocompatible. It enters the anterior chamber at the trabecular meshwork level and forms an aqueous lake beneath the conjunctiva and Tenon’s capsule 3 mm to 6 mm posterior to the limbus.

Douglas Baker, MD, and colleagues have presented 1-year results from a 2-year study to assess the safety and effectiveness of stand-alone MicroShunt surgery (Figure 1) versus trabeculectomy in patients with POAG.

The randomized, single-masked study was conducted at 29 sites, 24 of which were in the United States. Patients were between the ages of 40 and 85 years with POAG and were on the maximum tolerated amount of glaucoma medications. The exclusion criteria were previous conjunctival incisional surgery, aphakia, angle closure, and secondary open-angle glaucomas such as post-trauma, pseudoxfoliation, or pigment dispersion.

**KEY EFFECTIVENESS END POINTS**

The primary outcome the investigators were looking for was a reduction in IOP of 20% or greater at 1 year, without increasing the number of medications from baseline. They measured IOP over time, number of glaucoma medications, adverse events (AEs), incidence of persistent hypotony, postoperative interventions, and corneal endothelial cell density.

For the procedure (Figure 2), the conjunctiva and Tenon’s capsule were removed at the limbus as a unit. The mytomycin (0.2 mg/mL)–soaked Weck-Cel sponge was placed on the sclera and beneath the Tenon’s for 2 minutes. The initial incision in the sclera is 3 mm posterior to the limbus, and the blade enters the anterior chamber at the trabecular meshwork level.

Within the overall study population, the primary effectiveness end point was met 53.9% of the time with the MicroShunt and 72.7% of the time with trabeculectomy. If the focus is placed on the group with IOP 21 mm Hg or greater, the MicroShunt met the primary end point 63.8% of the time and trabeculectomy 75% of the time.

Looking at the mean IOP over time, starting at baseline at 21.1 mm Hg, at 1 year the mean in patients with the MicroShunt was 14.2 mm Hg and with the trabeculectomy, 11.2 mm Hg. The mean number of glaucoma medications was 3 at baseline, and after intervention at the end of 1 year, 0.6 medications for the MicroShunt and 0.3 for the trabeculectomy.

**ADVERSE EVENTS**

There was a 5.2% loss in corneal cell density with the MicroShunt, and a 6.9% loss with trabeculectomy. Persistent ocular hypotony occurred 3.0% of the time with the MicroShunt and 9.9% with trabeculectomy. Cataract progression was seen 12.2% of the time in patients with the MicroShunt and 14.5% in those who had trabeculectomy. Choroidal effusion occurred in 4.8% of those with the MicroShunt and in 7.6% with trabeculectomy.

Postoperative interventions included suture lysis and medication change, occurring in 40.8% of patients with the MicroShunt and in 62.4% of those who received trabeculectomy. There were no reports of endophthalmitis in either group at 1 year.

**CONCLUSIONS**

This was a prospective randomized study conducted in patients with primary open-angle glaucoma taking the maximum-tolerated number of glaucoma medications. Both trabeculectomy and MicroShunt surgery resulted in a reduction in intraocular pressure and supplemental glaucoma medications at 1 year.

By Steve Lenier; Reviewed by N. Douglas Baker, MD
EYELID

(Continued from page 1)

of scar tissue,” Alford said. “Studies have shown that the material decreases dermal fibrosis.”

Matristem is a xenograft, a material derived from animal tissue. Other commercially available xenograft materials include Integra Bilayer Wound Matrix (Integra LifeSciences Corp) produced from bovine collagen, shark, and silicone; OASIS Wound Matrix (Healthpoint Ltd) from porcine jejunal; and Matriderm (MedSkin Solutions Dr Suweland AG) from bovine ligaments.

In contrast, allografts, which are derived from human tissue, include products such as AlloDerm Regenerative Tissue Matrix (LifeCell) and Dermagraft (Organogenesis, Inc).

PERIOCULAR RECONSTRUCTION EXPERIENCE WITH THE ACELL MATRIX

Alford’s initial experience included reconstructive procedures in 17 patients (11 women, 6 men), specifically, 14 with periorcular Mohs defects, and 1 each with epidermolysis bullosa, cicatricial ectropion, and a skin graft donor site. The patients ranged in age from 36 to 84 years.

Alford described some illustrative cases. A 47-year-old patient had periorcular epidermolysis bullosa refractory to conventional wound care over 2 years. Epidermolysis bullosa is characterized by a defect in laminin. Alford chose to use the ACell product because laminin is 1 of the glycoproteins supplied. The lesions healed after application of the urinary bladder matrix.

Another case involved a 66-year-old patient with a large, superficial Mohs defect of the brow. At 6 weeks postapplication, the skin was completely healed and eyebrow cilia were growing.

These patients showed significant improvement of their skin lesions. The ideal locations for use of ACell xenograft products are medial and lateral canthal defects, preauricular skin graft donor sites, and the superior rim and brow defects. Further experience with the material has shown that defects in the central lower eyelid need additional procedures such as lid lightening. Eyelid margin defects have not been studied.

STANDARD APPLICATION PROCEDURE

Alford now has experience with more than 40 patients and has standardized his application protocol. The material is available as Cytal Wound Matrix sheets of various sizes and thicknesses and as MicroMatrix powder.

First, the powder is moistened with a small amount of sterile erythromycin ointment and normal saline to create a workable paste. After a sterile prep, the powder is applied over the defect. After a sterile prep, the material is sutured in place with a 6-0 chromic suture. The sheet is bolstered and patched with a light dressing such as a bandage.

TAKE-HOME

◗ Urinary bladder matrix, a skin substitute material made from porcine bladder, can be used successfully in periorbital reconstructive procedures.

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Dr Alford has no financial disclosures related to this content.

STENT

(Continued from page 10)

implantation resulted in a reduction in IOP and supplemental glaucoma medications at 1 year.

In the MicroShunt group, 53.9% of patients experienced a 20% or greater decrease in mean diurnal intra-operative pressure from baseline to year 1. This increased to 63.8% in the group that had IOP 21 mm Hg or greater when they entered the study. There was a reduction in mean diurnal IOP, from 21.1 mm Hg at baseline to 14.2 at 1 year.

The mean number of medications decreased from 3.1 to 0.6 at 1 year and 71.6% of patients were medication free at 1 year. Incidents of AEs and corneal endothelial cell loss were similar between the 2 groups, and there were no reports of endophthalmitis at 1 year.

PRACTICAL APPLICATIONS

The study provides 1-year data on the MicroShunt from 29 sites in the United States, the Netherlands, Spain, Italy, France, and the United Kingdom. Patients with POAG on maximum-tolerated medical therapy (baseline IOP, 15-40 mm Hg) and no previous history of conjunctival surgery were included. In the study, patients with uncontrolled POAG who underwent MicroShunt implantation achieved, on average, IOP of less than 15 mm Hg up to 1 year after surgery.
New molecule for allergic conjunctivitis makes debut

First new therapy in nearly a decade offers another option for physicians, patients

By Richard Teofilo Atallah and Richard D. Najac, MD, FACS; Special to Ophthalmology Times

The FDA recently approved the first prescription-only topical ocular formulation of the second-generation antihistamine cetirizine for the treatment of ocular itching associated with allergic conjunctivitis.

Cetirizine ophthalmic solution 0.24% (Zerviate, Nicox Ophthalmics Inc; licensed to Eyevance Pharmaceuticals, LLC) demonstrated robust efficacy in 3 randomized, double-masked, placebo-controlled clinical trials using the Ora Conjunctival Allergen Challenge (CAC) model among patients with allergic conjunctivitis.

Two of the trials that evaluated onset and duration showed that cetirizine ophthalmic solution led to statistically and clinically significantly less ocular itching versus vehicle at 15 minutes and 8 hours after treatment.⁵ The ophthalmic solution breaks the 10-year drought since the last approval for allergic conjunctivitis treatment, with the twice-daily drops hitting the market in March 2020.

Cetirizine hydrochloride (Zyrtec, Johnson & Johnson Consumer) is recognized as the number 1 oral antihistamine allergy treatment recommended by allergists, with 23 years on the market and countless doctor and patient years of experience.⁶ Based on its vast track record of therapeutic success and safety in different formulations, the industry sought to develop cetirizine as an ophthalmic solution.

BACKGROUND

Allergic conjunctivitis affects at least 30% of Americans.⁴ Reactions range anywhere from mild—making it merely a self-limiting nuisance—to the other end of the spectrum, when allergies become a debilitating disease, causing patients to have a significantly impaired quality of life. Stimuli, whether tree and grass pollens, animal hair and dander, or any number of other environmental insults, manifest in the familiar cascade of ocular symptoms that include itching, redness, chemosis, tearing, and eyelid swelling.

Thanks to the vast work being done around ocular surface disease and dry eye—along with fine-tuning of diagnostic and treatment algorithms—awareness among eye care specialists to diagnose and treat the “red eye” is improving. Allergic conjunctivitis is a frequent and substantial piece of the puzzle when it comes to finding the root cause of ocular surface disease.

Patients with allergies typically have bilateral signs and symptoms, with the most common ocular symptoms being itching, burning, redness, and tearing. Allergic conjunctivitis is often associated with swelling, an important area of differentiation from dry eye disease. Eversion of the lower lid is highly advised to assess the extent of chemosis.

ALLERGY CYCLE

In response to an allergen, the process of conjunctivitis has an early acute phase followed by a late phase. Allergens interact with immunoglobulin E, which is bound to sensitized mast cells that in turn activate increased histamine and subsequent degranulation.⁴ The release of histamine and other proallergic mediators during the acute phase induces itching, vasodilation, and vascular leakage. This is followed by ocular redness, chemosis, and lid swelling. Mast cells then synthesize, releasing cytokines, chemokines, and growth factors, which kicks off a cascade of inflammatory events. During the final late-phase reaction, eosinophils, neutrophils, and macrophages infiltrate conjunctival tissues.⁵,⁶

The commonly used and approved treatments for ocular allergies include antihistamines and mast cell stabilizers, or both; and these agents act to reduce the signs and symptoms of the early-phase reaction.⁷,⁸

OCULAR FORM OF CETIRIZINE

Cetirizine is a second-generation antihistamine (highly selective H₁ receptor antagonist) that binds competitively to histamine receptor sites to reduce swelling, itching, and vasodilation. Two phase 3 efficacy studies revealed strong and similar anti-itch efficacy of cetirizine ophthalmic solution 0.24% compared with vehicle (using the CAC model).

The single-center (study 1) and multi-center (study 2), double-masked, randomized, vehicle-controlled, parallel group CAC studies were conducted over approximately 5 weeks and 4 study visits. Patients with moderate and severe symptoms were enrolled in the trials, and study 2 required patients to have more severe allergic conjunctivitis symptoms. Subjects were screened for an allergen response at visits 1 and 2 and then randomized at visit 3. Approximately 100 subjects were randomly assigned in each study. The primary efficacy end points were ocular itching and conjunctival redness 15 minutes and 8 hours posttreatment, post-CAC.

Allergists, with 23 years on the market and counting, consider cetirizine to be the “red eye” is improving. Allergic conjunctivitis makes debut

By Richard Teofilo Atallah and Richard D. Najac, MD, FACS; Special to Ophthalmology Times

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Take-home

» Cetirizine ophthalmic solution 0.24% is a therapeutic with an ability to quickly quell ocular itching for patients experiencing allergic conjunctivitis. There are no safety concerns identified with cetirizine treatment.

QUELLS ITCHING FAST

Investigators administered cetirizine 15 minutes or 8 hours before CAC, and subjects had significantly lower ocular itching at all time points post-CAC (P < .0001) compared to vehicle in both studies. The investigators’ assessment of conjunctival redness was significantly lower after cetirizine treatment compared to vehicle at 7 minutes post-CAC and at both 15 minutes and 8 hours posttreatment in both studies (P < .05).

Numerous secondary end points, ocular and nasal, were also examined.

It should be noted that the most robust treatment differences were observed in study 2, where patients were required to have more severe symptoms in order to be included (P < .05). Investigators identified no safety concerns for cetirizine ophthalmic solution 0.24%.

CONFORT IS KEY

For added comfort, cetirizine ophthalmic solution 0.24% is designed with Hydraflex, which includes glycerin and hydroxypropyl methylcellulose, ingredients commonly found in lubricant drops. Patients in the FDA trials reported a mean comfort score of less than 1 at all time points (on a scale of 1-10, with 1 being the most comfortable). The solution is also formulated with a neutral pH of 7.0, similar to the natural tear film.

Continues on page 13 : Molecule
The dropless future: SLT as a first-line treatment for glaucoma

Drop tolerance, adherence remain challenges for physicians, patients

By Kristin O. Chapman MD; Special to Ophthalmology Times®

FROM TIMOLOL TO rho kinase inhibitors, glaucoma medications for primary open-angle glaucoma (POAG) have steadily progressed for decades. Drop tolerance and adherence are challenges that physicians and their patients have wrestled with for years. But with advances in laser technology improving laser safety and recent research demonstrating selective laser trabeculoplasty (SLT) jefficacy and safety, drops do not have to be the first line of treatment. Now, we can offer SLT with confidence as first-line therapy to control pressure and avert the challenges and unpredictability associated with glaucoma drops.

DROPS: COMPLAINTS AND CLINICAL CONCERNS

For every familiar problem associated with glaucoma drops, there are hidden complexities. The most pronounced problem is chronic toxicity and inflammation of the ocular surface induced by medications and their preservatives. Patients cannot feel glaucoma, but they can feel dry eye symptoms. As their eyes get red, dry, and uncomfortable, patients may stop using glaucoma drops to relieve their symptoms, and their pressure suffers. What’s more, we know that progressive ocular surface disease (OSD) can decrease the efficacy of glaucoma surgery, such as trabeculectomy, if needed down the road.

MOLECULE

(Continued from page 12)

CONCLUSION

Eye-care providers now have a solution for patients with allergic conjunctivitis experiencing disruptive ocular itching. The drop form of cetirizine ophthalmic solution 0.24% gives eye care providers a chance to greatly improve patients’ quality of life with an effective and targeted approach. Notably, unlike some oral antihistamines, the new formulation did not cause drowsiness.

Cetirizine ophthalmic solution 0.24% is a strong therapeutic with an ability to quickly quell ocular itching for patients experiencing allergic conjunctivitis. There are no safety concerns identified with cetirizine treatment. Drop comfort is rated as “very comfortable.”

REFERENCES

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ORACLE MODEL KEY TO ESTABLISHING DRUG EFFICACY

IT HAS BEEN A STRUGGLE for researchers to measure allergic conjunctivitis in a controlled environment. There is a huge amount of variability owing to numerous factors such as allergen, subject, season, and weather, resulting in different symptomatic responses and a range of severity. The Ora conjunctival allergen challenge (CAC) model circumvents these concerns, inducing a moderate to severe allergic reaction in a controlled and reproducible manner.

In the Ora-CAC model, all subjects undergo a screening procedure where they demonstrate reproducible moderate to severe allergic responses. This model is an established method approved by regulatory agencies to determine therapeutic efficacy in the relief of allergic signs and symptoms. Numerous studies have demonstrated the clinical efficacy of therapeutics for the indication of allergic conjunctivitis using this model.


MAKING PROGRESS: FROM TIMOLOL TO rho kinase inhibitors, glaucoma medications have steadily progressed for decades. But with advances in laser technology improving laser safety and recent research demonstrating selective laser trabeculoplasty (SLT) jefficacy and safety, drops do not have to be the first line of treatment. Now, we can offer SLT with confidence as first-line therapy to control pressure and avert the challenges and unpredictability associated with glaucoma drops.

RICHARD D. NAJAC, MD, FACS

RICHARD D. NAJAC, MD, FACS is a second-generation ophthalmologist practicing in Queens, New York, for more than 20 years. Dr Najac is an investor of Eyevance.

RICHARD TEOLFILO ATALLAH, PGY-3

Richard Teofilo Atallah, PGY-3, is a third-year medical student at Rutgers New Jersey Medical School in Newark, New Jersey, and has no financial disclosures related to this product.
INJECTIONS

(Continued from page 1)

understand any potential risk for similar kinds of injury to the eye.”

Because of these concerns, Rosen, the senior investigator, and his team undertook a retrospective observational clinical study in which they measured retinal perfusion density changes on optical coherence tomography angiography (OCTA) and thickness changes on OCT that were associated with acutely increased IOP after intravitreal injections.

The study, which included 40 eyes of 39 patients, was conducted at a tertiary care center in New York from October 2016 to June 2017. Patients were included who were 18 years and older, had vision exceeding 20/100, could fixate, had no media opacities, and were treated with bevacizumab (Avastin, Genentech, Inc) or aflibercept (Eylea, Regeneron Pharmaceuticals, Inc) to treat diabetic retinopathy (DR), retinal vein occlusions (RVOs), age-related macular degeneration, retinal neovascularization, or radiation retinopathy. The investigators analyzed the perfusion density on OCTA, thickness density on OCT, and IOPs were measured before and after the injections. Patients typically regain vision because the IOP decreases toward normal and blood flow returns to the macula.”

They also hypothesized that the increased OCT thickness nasally may result from redistribution of fluid or fluid shifts that occur when the IOP changes.

“Doctors always have to weigh the benefits of any treatment with risks to the patient,” Barash said. “If we are inadvertently causing damage to ocular structures with our injections, we should make sure that all physicians performing the procedure are aware of possible [adverse events] so they can discuss these with patients and work to minimize the risks of these treatments.”

The investigators warned of the possibility that regular intravitreal injections may be sustaining perfusion-related injury to ocular structures that may produce glaucomatous damage to the macula and optic nerve. This newfound information can lead doctors to use advanced imaging and visual field testing to look for early signs of damage and perhaps lead to changes in the way ocular diseases are treated. They suggested that the study results could pave the way for doctors to pretreat patients with medications to reduce the IOP spikes after receiving injections to prevent possible long-term damage. The investigators may also promote more careful consideration of the risks in patients with advanced glaucoma before administering injections.

REFERENCES


TAKE-HOME

» Research has found that chronic intravitreal injections may lead to ocular damage.

‘Doctors always have to weigh the benefits of any treatment with risks to the patient.’

- Alexander Barash, MD

Patient age was significantly (P = .018) associated with the overall decreased superficial macular perfusion. The investigators published their findings in Retina. The investigators commented that the decreased angiographic perfusion density “… that is associated with increased IOP likely contributes to the acute decrease in visual acuity experienced immediately after injections. Patients typically regain vision because the IOP decreases toward normal and blood flow returns to the macula.”

‘Take-home’

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“Doctors always have to weigh the benefits of any treatment with risks to the patient,” Barash said. “If we are inadvertently causing damage to ocular structures with our injections, we should make sure that all physicians performing the procedure are aware of possible [adverse events] so they can discuss these with patients and work to minimize the risks of these treatments.”

The investigators warned of the possibility that regular intravitreal injections may be sustaining perfusion-related injury to ocular structures that may produce glaucomatous damage to the macula and optic nerve. This newfound information can lead doctors to use advanced imaging and visual field testing to look for early signs of damage and perhaps lead to changes in the way ocular diseases are treated. They suggested that the study results could pave the way for doctors to pretreat patients with medications to reduce the IOP spikes after receiving injections to prevent possible long-term damage. The investigators may also promote more careful consideration of the risks in patients with advanced glaucoma before administering injections.

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REFERENCES


Study targets topical medication adherence, visual field progression
Research seeking benefits, options for open-angle glaucoma patients

By Steve Lenier; Reviewed by Donald S. Fong, MD, MPH

RESEARCH IS FOCUSING on topical medication adherence and visual field progression in open-angle glaucoma (OAG).

At the 2020 meeting of the American Glaucoma Society (AGS), Donald S. Fong, MD, MPH, of Kaiser Permanente Southern California (KPSC), presented a study designed to assess the effect of treatment adherence to topical glaucoma medications on visual field progression, using data from clinical practice. Not surprisingly, the study found that poorer medication adherence was significantly associated with a faster rate of visual field decline.

Elevated IOP is the only modifiable risk factor to reduce the risk of progression in OAG, and first-line treatment is typically topical ocular drops to lower IOP. “Low medication adherence may increase the risk of damage from glaucoma, but there is a lack of quantitative data on the relationship between treatment adherence and glaucomatous visual field progression,” Fong said.

REAL-WORLD STUDY
To address the lack of data, Fong and colleagues examined records from KPSC, an integrated health system that provides comprehensive care to over 4.6 million members. Fong noted several benefits of utilizing this population.

“In our integrated health system,” he said, “KPSC members receive their prescriptions from a single source, and patients tend to be long-term members of the health plan.” He explained that this allows for tracking patient refills, and makes long-term follow-up possible. The population is also representative of the state of California for racial diversity.

STUDY DETAILS
For the study, patients meeting inclusion criteria were stratified by severity of baseline visual field measurements, using readings from 6 months before and after the index date. For patients that had no visual field measurements in the time frame, their baseline disease severity was designated as “missing.”

Adherence was measured by proportion of days covered, which was determined as the number of days that the patient was supplied with medication, divided by the number of days in the period of interest. Patients who received multiple medications were considered adherent if 1 or more of their medications was filled, and adherence was reported in categories of low, moderate, and high.

The investigators hypothesized that the interaction between adherence and time would be positive. In other words, for a given follow-up time, patients with better adherence would have better mean deviation (i.e., less severe disease).

“Our study is the first to use real-world data to quantify the impact of non-adherence on glaucoma progression,” Fong said. “We demonstrated that treated glaucoma patients who were more adherent showed less loss of visual function. We need to improve patient adherence to medications because higher adherence will delay glaucoma progression and loss to a patient’s quality of life.”

SLT

(Continued from page 13)

SLT as First-Line Treatment
Since SLT was introduced by Lumenis in 2009, studies have demonstrated that it is safe, effective, and predictable. In 2019, the LiGHT study gave us the head-to-head comparison of SLT and drops that can give us the confidence to start recommending the procedure as a first-line treatment. In the LiGHT study, 718 patients were randomly assigned to SLT or medication.

Three years later, SLT patients hit their pressure targets at more visits than those with first-line eye drop therapy. Some patients taking drops required glaucoma surgery, but none of the SLT patients did. About 74% of SLT patients required no drops. In addition, in 97% of cases, SLT was more cost-effective than eye drops as a first-line therapy.

In my treatment paradigm for POAG, I start by discussing both SLT (Selecta Duet, Lumenis) and drops as first-line treatments. Patients are concerned most about the safety of SLT, pain during the procedure, and any restrictions on activities after treatment.

Although most patients elect to begin with an eye drop, educating patients about SLT at the beginning of their diagnosis is helpful in introducing non-drop therapies. If patients fail to reach their target pressure with their first-line drop treatment, I strongly recommend SLT before adding another drop.

In certain cases—such as pigmentary dispersion syndrome—I strongly recommend SLT before use of drops. For younger patients, I encourage them to proceed with SLT first so as to prevent decades of medication use and the associated cosmetic and ocular surface side effects. I also emphasize the value of SLT for patients with limited mobility or access to medications, such as people with inadequate prescription coverage and patients who are in care facilities or cannot administer drops independently.

CONCLUSION
Patients are counseled that while there is no pain during the procedure, the treated eye may be more sensitive to light or have a low-grade ache for 2 to 3 days after.

Overall, the procedure is well tolerated, and after SLT, most patients are surprised by the ease of the procedure and minimal postoperative symptoms. Patients who have spent years on drops often wish they had SLT sooner.

KIRSTIN O. CHAPMAN, MD
P: 626/951-6307
Dr. Chapman has no financial disclosures related to this content.
Investigators target algorithm for diagnosing glaucoma

Research finds automated segmentation software examines OCT scans

By Steve Lenier; Reviewed by Atalie C. Thompson, MD, MPH

In a study carried out by investigators at Duke University’s Vision, Imaging and Performance Laboratory, Atalie C. Thompson, MD, MPH, and colleagues developed a segmentation-free deep learning (DL) algorithm using the entire circle B-scan image from optical coherence tomography (OCT). The aim of the investigators was to determine if such an algorithm would be better at detecting glaucomatous damage than using the retinal nerve fiber layer (RNFL) value provided by the machine’s automated segmentation software.

According to the authors, glaucoma is usually diagnosed by a combined analysis of clinical parameters and risk factors such as age and IOP, tests for the evaluation of structural damage to the optic nerve, and visual function assessment with perimetry. Although this is generally accurate for diagnosing glaucoma, the algorithms may fail in the presence of segmentation errors (reported in 20% to 40% of scans). Even without segmentation errors, interpreting conventional SD-OCT RNFL information can be difficult, due to a large number of summary parameters in addition to maps and plots.

Recent advances in artificial intelligence have led to the development of DL algorithms, which can be trained to accurately detect complex patterns in images. These algorithms can learn to analyze information across an entire SD-OCT image rather than just a segment, and may potentially provide more information about the presence of glaucomatous damage than individual SD-OCT parameters from segmentation. Interpreting the whole image may minimize false positives that arise when clinicians assess multiple individual parameters.

This was a cross-sectional study of 1154 eyes in 635 individuals, and was undertaken to develop a segmentation-free DL algorithm to assess glaucomatous structural damage, using the whole peripapillary SD-OCT B-scan.

According to Thompson, the algorithm’s performance was compared with that of conventional RNFL thickness parameters.

A convolutional neural network was trained to discriminate glaucomatous from normal eyes using the SD-OCT circle B-scan without segmentation lines. The research team found the DL algorithm had a greater area under the receiver operating characteristic curve than RNFL global and sectoral parameters, and it was more sensitive at 80% and 95% specificity. This appeared to be even more likely in early disease.

The authors noted some limitations. Although they used an independent test dataset for the final assessment of diagnostic accuracy, external validation in populations from other clinical settings is desirable.

In addition, it should be noted that the diagnosis of glaucoma is not based on the results of a single test but rather on a combined interpretation of information on risk factors, such as age and intraocular pressure, and results of structural and functional tests. Therefore, it remains to be seen how incorporating such an algorithm would affect clinical diagnosis when combined with these other pieces of information acquired in clinical practice, as well as for assessing change over time.

The authors concluded that the segmentation-free DL algorithm they developed performed better than global and sectoral RNFL thickness parameters for discriminating glaucomatous from control eyes, especially in cases of preperimetric or early perimetric glaucoma. They believe that using this DL algorithm in a clinical setting may improve the accuracy and sensitivity of SD-OCT for diagnosing glaucoma, while obviating the need for error-prone segmentation of retinal layers. Future studies should investigate how such an approach contributes to diagnostic decisions when combined with other relevant clinical information, such as risk factors and perimetry results.
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ST laser therapy may reduce DME intravitreal injections

With an excellent safety profile, option may be a reasonable treatment approach

By Pauline T. Merrill, MD; Special to Ophthalmology Times*

Data courtesy of Pauline T. Merrill, MD

**Table 1. Study Demographics**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63 ± 13 (range, 35-78)</td>
</tr>
<tr>
<td>Gender</td>
<td>53% male, 47% female</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>67% Caucasian, 20% Latino, 13% African American</td>
</tr>
</tbody>
</table>

Based on these results, ST laser therapy could provide an adjunctive treatment option for patients with CSME, with a safer risk profile compared with the standard ETDRS CW focal laser treatment or anti-VEGF or steroid injections alone.

For CSME treatment, my colleagues and I have been offering the addition of ST laser therapy combined with CW focal laser treatment where indicated, in hopes of reducing the number of intravitreal injections patients may need while maintaining excellent visual and anatomic outcomes.

**STUDY: ADJUNCTIVE TREATMENT WITH ST LASER THERAPY**

With institutional review board approval, we performed a retrospective chart review of patients with at least 6 months follow-up after adjunctive treatment with the ST laser.

End points included best-corrected visual acuity (BCVA) (in logMAR), central foveal thickness (CFT), and macular volume. Values were reported at baseline and at a 6-month follow-up.

In addition, the number of intravitreal injections during the 6 months before baseline was compared with the number of treatments (intravitreal injections and/or additional lasers) during the 6 months after baseline. All statistics were performed with a spreadsheet program (Microsoft Excel).

Means before and after baseline were compared with paired t tests.

All treatments were performed using a laser (Smart532, Lumenis) featuring a multi-wavelength photoagulator with green wavelengths.

In eyes with focal extrafoveal leakage on fluorescein angiography, extrafoveal microaneurysms were treated in the CW mode; the laser signal consisted of a single pulse with a duration of 50 to 100 msec.

The spot size was 50 to 100 μm. Power was titrated to obtain a light-gray end point, usually between 90 to 140 mW.

Areas of leakage identified on fluorescein angiography and thickening on optical coherence tomography (OCT) were treated with ST laser ther-

**RESEARCH**

In 2009, a study comparing ST micropulse laser treatments with CW focal laser for CSME showed the ST treatment proved to be equally effective with less retinal scarring.11

In 2011, a randomized controlled study of 125 patients showed greater improvement in functional and anatomical outcome measures with high-density ST micropulse laser treatment compared with the modified ETDRS focal/grid laser.12

**TAKE-HOME**

> Used as an adjunct, ST laser therapy may reduce the treatment burden for patients while maintaining visual acuity.
apy, using the SmartPulse mode.

In this mode, each pulse consisted of a train of brief (100 ms) subpulses, delivered at a duty cycle of 5%, with a 200-µm spot size. A titration procedure was also performed to determine the power.

Starting in the CW mode, a single spot was applied in an extrafoveal area, using an initial power of 80 mW and gradually increasing it until a gray response was obtained.

Next, the laser was switched to SmartPulse mode, and the power was multiplied by 3 (up to a maximum of 400 mW). With these settings, the tissue reaction was subthreshold. A scanner was used to deliver 3 x 3 patterns with a spacing of 0.25 spot size. Patterns were overlapped to ensure contiguous treatment.

During the 6 months after baseline testing, eyes were evaluated to determine whether they were stable or improving or if further treatment was needed.

Additional treatment could be an intravitreal anti-VEGF, a steroid injection, or an additional ST laser treatment.

**Table 2. Comparison of Baseline (Prelaser) and 6-Month Follow-Up**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Baseline (Prelaser)</th>
<th>6-Month Follow-Up (Postlaser)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogMAR (m ± SD) [range]</td>
<td>0.56 ± 0.4 [0.1-1.6]</td>
<td>0.58 ± 0.43 [0.1-1.7]</td>
<td>.584</td>
</tr>
<tr>
<td>CFT in mm (m ± SD) [range]</td>
<td>297 ± 82 [117-423]</td>
<td>298 ± 82 [184-474]</td>
<td>.478</td>
</tr>
<tr>
<td>No. anti-VEGF injections (m ± SD) [range]</td>
<td>2.3 ± 1.64 [0-4]</td>
<td>0.65 ± 0.81 [0-2]</td>
<td>.00019</td>
</tr>
<tr>
<td>No. Intravitreal injections (anti-VEGF and/or steroids) (m ± SD) [range]</td>
<td>2.4 ± 1.64 [0-4]</td>
<td>0.7 ± 0.8 [0-2]</td>
<td>.00011</td>
</tr>
<tr>
<td>No. any treatment (injections or additional laser) (m ± SD) [range]</td>
<td>2.4 ± 1.64 [0-4]</td>
<td>0.8 ± 0.77 [0-2]</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Data courtesy of Pauline T. Merrill, MD

**Follow-up treatment, the number of injections decreased by more than half, while visual acuity and central retina thickness were maintained.**

- Pauline T. Merrill, MD

**FUTURE OUTLOOK FOR ST LASER THERAPY**

In this retrospective study of patients with DME treated with the Lumenis Smart532 laser, there was a good safety profile. Following treatment, the number of injections decreased by more than half, while visual acuity and central retinal thickness were maintained. This decrease in treatment burden is encouraging for patients.

Most studies of anti-VEGF treatment for CSME (eg, RISE/RIDE,¹³ Restore,¹⁴ VISTA/VIVID,¹⁵ and PROTOCOL T of the Diabetic Retinopathy Clinical Research network¹⁶) excluded patients with very...
OCT

(Continued from page 19)

good vision and/or mild macular edema.

ST laser therapy is of particular interest for investigators in light of Diabetic Retinopathy Clinical Research Protocol V. Patients with 20/25 or better vision and CSME treated with observation only, CW focal laser, or aflibercept (Eylea, Regeneron) showed no significant differences in visual acuity at 2 years, but there was a trend toward better vision with laser or aflibercept, compared with observation.13

Conclusion

Given the excellent safety profile of the ST laser, this may be a reasonable treatment approach in such patients, either alone or in combination with a CW focal laser.

It is encouraging to find that ST laser therapy may help reduce the treatment burden for patients with DME by decreasing the number of intravitreal injections needed, while maintaining visual acuity.

Randomized prospective studies are needed to further elucidate the merits of this approach.

References


Pauline T. Merrill, MD

Dr Merrill is a partner at Illinois Retina Associates, as well as associate professor and section director for uveitis, Rush University, Chicago. She has received numerous honors, including the American Academy of Ophthalmology Achievement Award and the American Society of Retina Specialists Senior Honor Award.

Dr Merrill reports research grants funding from Alimera, Lumenis, the National Eye Institute, and Santen, and has served as a consultant with Allergan Sciences, Genetech, Graybug, Lumenis, and Santen. The author thanks Yair Manor, PhD, clinical director, BU Vision, for his assistance with the study and statistical analysis.
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 adjacent page.

BAK=benzalkonium chloride.

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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.
The eye and COVID-19: 
Providing facts, not fears

Details help pave way for clinicians to provide safe environments for their patients

By Lynda Charters; Reviewed by Ella Faktorovich, MD

A GREAT DEAL of information and misinformation has been in the news about coronavirus disease 2019 (COVID-19) since the disease began to spread rapidly in early 2020. The best way to sort out the wheat from the chaff, according to Ella Faktorovich, MD, is to rely on studies in the scientific literature to answer questions about transmission.

“One of the best ways to make the case about the virus and the eye need to be answered. This will determine the best ways to assure patient care safely and effectively.”

Faktorovich is founder of Pacific Vision Institute in San Francisco, California, and the annual San Francisco Cornea, Cataract, and Refractive Surgery Symposium.

Those questions are: What is the incidence of conjunctivitis in patients with COVID-19? Can the ocular surface serve as a reservoir of virus possibly transmissible to others? Can the ocular surface serve as a portal of entry for COVID-19 virus through aerosolized droplets or hand-eye contact? Determining the answers will pave the way for clinicians to provide the safest environment for patients and staff.

To answer the above questions, Faktorovich and her research team performed PubMed, bioRxiv, and medRxiv database searches and analyzed the results of studies in peer-reviewed publications (PubMed) and in scientific preprints (bioRxiv, medRxiv) on COVID-19, coronaviruses, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

LITERATURE REVIEW

Two studies, one in the New England Journal of Medicine (2020;382:1708-1720) and the other in medRxiv (https://doi.org/10.1101/2020.02.11.20021956), reported that the incidence of conjunctivitis is low (respective ranges, 0.8% in a study of 1099 patients with confirmed virus examined by nonophthalmologists to 4.68% in a study of 534 symptomatic patients with confirmed virus examined by ophthalmologists).

A case report in the British Journal of Ophthalmology (http://dx.doi.org/10.1136/bjo.2020-316304) described a patient who presented with bilateral acute conjunctivitis 13 days after symptom onset. Polymerase chain reaction identified the presence of viral RNA isolated from conjunctival swabs.

A case report in the Annals of Internal Medicine (https://doi.org/10.7326/M20-1176) described a patient with viral RNA isolated from conjunctival swabs who presented with conjunctivitis 1 day after symptom onset. COVID-19 was confirmed by nasopharyngeal swab.

A study of 30 patients with confirmed COVID-19 diagnosis in the Journal of Virology (https://doi.org/10.1002/jmv.25725) found that only 1 patient had conjunctivitis. Viral RNA was isolated from his conjunctiva. Twenty-nine patients without conjunctivitis were negative for COVID RNA but had sputum tests positive for COVID. Two other reports on medRxiv (doi: https://doi.org/10.1101/2020.02.26.20027938 and doi: https://doi.org/10.1101/2020.02.11.20021956) also described similar findings.

In one of the reports, 2 of 72 patients with confirmed COVID-19 diagnosis had conjunctivitis, 1 of whom tested positive for viral RNA in their conjunctiva. Patients without conjunctivitis tested negative for viral RNA in their conjunctiva. Additionally, conjunctivitis may be the first presenting sign of COVID-19, with the other—illike symptoms—quickly following.

The message from this review is that the presence of conjunctivitis should be highly suspicious for the presence of the COVID-19 virus. The examiner should treat these patients as highly infectious, with very high likelihood that they are shedding virus from their ocular surface. However, patients without conjunctivitis, even if they have other COVID-19 symptoms and should also be treated as highly infectious, are unlikely to harbor viral RNA on their ocular surface.

However, this raises the question about the low incidence of conjunctivitis compared with respiratory tract infection. Faktorovich pointed out that the density of ACE2 receptors on the ocular surface may be at least 30% lower than in other tissues (Clinical and Experimental Optometry https://doi.org/10.1111/ cxo.13088).

“In addition to ACE2 and TMPRSS2, coronaviruses may need heparan sulfate coreceptors, such as CD209, for example, on the cell surface to facilitate viral binding, especially for highly pathogenic virus, such as SARS-CoV-2. Such receptors have been detected on the eye. They are located, however, on corneal dendritic cells and conjunctival fibroblasts, which lie beneath the ocular surface and are not immediately accessible to the virus (Current Eye Research https://doi.org/10.3109/02713683.2012.696172).

There also are proteins in human tears, lactoferin and 9-O-acetylated sialic acid, that can bind the virus, thereby potentially preventing its attachment to the ACE2 receptor (Glycobiology https://doi.org/10.1093/glycob/cw041), Faktorovich said.

“The ocular surface may also be protected by the ‘good’ bacteria living there and comprising a unique microenvironment called the ocular microbiome,” Faktorovich said, referencing a pioneering article by Anthony St. Leger, PhD (Immunity 2010.10161/j.immuni.2017.06.014). In this article, he identifies the microbiome on the ocular surface and its effects on the eye’s immune homeostasis and defense against pathogens.

HOW THE VIRUS WORKS

Angiotensin-converting enzyme 2 (ACE2) receptors and TMPRSS2 proteins are the portals on the surface of human cells by which the virus enters the cells. Faktorovich explained that these receptors are part of the renin-angiotensin system that is instrumental in regulating fluid and electrolyte homeostasis.

In addition to their presence in lung, intestine, kidney, blood vessels, heart, and brain tissue, they have been identified in the trabecular meshwork, ciliary body, retina, and in human corneal epithelial and conjunctival cells (Journal of Clinical Medicine https://doi.org/10.3390/jcm9051269; https://doi.org/10.1101/2020.05.09.086165; https://doi.org/10.1101/2020.05.09.086165).

‘As we begin to reopen our eye care practices, key questions about the virus and the eye need to be answered.’

Ella Faktorovich, MD

TAKE-HOME

During examinations, good hand hygiene and a face mask are still important for both the patient and the examiner.

Details help pave way for clinicians to provide safe environments for their patients

JUNE 15, 2020 :: Ophthalmology Times®

Continues on page 24 : Facts
FACTS

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“The eye’s microbiome may keep the number of ACE2 receptors low and the amount of lactoferrin high to protect the eye against the virus,” said St. Leger, assistant professor of ophthalmology and immunology at the University of Pittsburgh School of Medicine in Pennsylvania.

THE 3 IMPORTANT QUESTIONS

Returning to the previously mentioned questions, the conjunctival incidence in published studies is low. The conjunctivitis found in these patients is a typical mild to moderate viral follicular conjunctivitis with conjunctival injection and watery discharge. Conjunctivitis can be either the first presenting sign of COVID-19 or present later in the disease course, with a duration of 4 to 7 days.

Regarding the question of the eye as a potential viral reservoir, 5 of 6 patients with conjunctivitis had conjunctival swabs positive for viral RNA. Only 1 of 161 patients with COVID-19 and no eye symptoms had a positive conjunctival swab, but that patient had other symptoms of viral infection, including fever and cough.

Regarding the question of the ocular surface being a portal of entry for COVID-19 virus, the potential exists, but that has not been proved. Although the ocular surface has receptors that the virus uses to initiate its attachment to a human cell, other components of the ocular surface may prevent viral attachment and entry.

Faktorovich pointed out that the virus may potentially travel from the ocular surface to the respiratory tract mucosa via the nasolacrimal duct. A small animal study reported mild interstitial pneumonia after conjunctival was inoculated with a very large inoculum (https://doi.org/10.1101/2020.03.13.990036). However, viral transmission via the eyes has not been proved in humans.

RECOMMENDATIONS

Faktorovich said she believes that questions about ocular symptoms should be added to the other questions about systemic symptoms asked of patients during screening before they enter the clinic. The ocular questions should include specific references to eye redness, tearing, discomfort, foreign body sensation, and discharge.

“Clinicians have to decide whether their clinic can care for patients with a high probability of shedding the virus or whether they should be triaged to a center fully prepared to safely manage such patients,” Faktorovich suggested.

Faktorovich also advised physicians to assume a patient has COVID-19 if they have conjunctivitis and that they will be shedding virus from their ocular secretions and are, therefore, contagious. In this case, physicians will need more than hand sanitizer and a mask.

“Clinicians should wear gloves when examining such patients and then immediately discard the gloves using the same precautions as when discarding highly contagious waste material,” Faktorovich said. “Clinicians should assume that symptomatic patients have virus in their nasopharyngeal secretions and that the virus likely will be aerosolized when they speak. Therefore, wearing an N95 mask and tight-fitting goggles is essential.”

Examiners should also instruct patients to not speak when they are in close proximity to the physician or examiner.

However, if patients have neither systemic nor ocular signs and/or symptoms suggestive of COVID-19, the probability of their harboring the virus on their ocular surface is very low. During examinations of such patients, good hand hygiene and use of a face mask are still important for both the patient and the examiner, but goggles and respirator masks may not be necessary. A recent review in Frontiers of Public Health (2020 https://doi.org/10.3389/fpubh.2020.00155) recommends using chlorhexidine/alcoholic hand rub rather than alcohol alone.

“Hopefully, this fact-based information will help reduce the stress experienced by eye care providers and staff members about how to examine patients,” Faktorovich concluded.

REFERENCES


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Dr Faktorovich has no financial interest in this subject matter.

Facts vs Myths Surrounding the COVID-19 Virus


FACT: Although no published data are available yet on how ultraviolet light affects the COVID-19 virus specifically, its effect on other SARS viruses has been studied.

MYTH: Any face covering will protect against the virus.

FACT: Scarves and bandanas made of a thin fabric or a single fabric layer will not be as effective in reducing virus transmission as those that have a filter or are folded 3 to 4 times to provide a better barrier.

MYTH: Wearing gloves will provide protection from the virus.

FACT: Gloves will be effective if the wearer discards them after touching something that may be contaminated. After use, the gloves must be removed properly by peeling them from hands so they are inside out, to prevent contacting the contaminated outer surface.

MYTH: All hand sanitizers are the same, and the higher the alcohol content, the better the sanitizer will work against the virus.

FACT: The alcohol content of commercially available hand sanitizers has to be at least 60% for ethyl alcohol and 70% for isopropyl alcohol to work against the virus. Alcohol content over 80% evaporates too quickly and does not stay on the skin long enough to kill the virus. Hand sanitizers need to specify the type of alcohol they contain. A hand sanitizer showing simply alcohol does not guarantee that it will kill the virus.

MYTH: Wearing shoe covers will provide protection from the virus.

FACT: Shoe covers are effective only if an individual knows the proper way to put them on and remove them to avoid contamination. Lack of training may cause the wearer to inadvertently touch the contaminated area.
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Strategies for coping with physician depression during COVID-19

Medical practitioners face emotional burden, other hurdles from pandemic

By Rebekah Bernard, MD

Physicians, just like the patients we serve, are facing an unprecedented emotional burden from the COVID-19 pandemic. First-line responders are at especially high risk of experiencing psychological hardship from the burden of disease, death and anxiety, whereas physicians not on the front lines are feeling the strain of worried patients, financial hardship and uncertainty about the future.

Increased emotional stress during this time may also increase the risk of physician depression. An estimated 300 to 400 physicians take their own lives each year.

Emotional contagion

Emotions, just like viruses, are contagious. Psychologist and author Steven Cohen, Psy.D., notes that doctors, just like all others, are at risk of internalizing the negative feelings of the people around them. Physicians who work in a daily atmosphere of severe emotional distress and fear must take special precautions to avoid being overwhelmed by negative emotions.

According to Cohen, the first step to managing emotional distress is to simply acknowledge and examine our emotional reactions. Physicians often experience guilt, anxiety or shame when we experience powerful emotions like sadness or anger. This discomfort prompts us to try to repress these feelings. Cohen says that it’s essential to acknowledge and reflect on these feelings.

The simple act of labeling our emotions can be a powerful tool in coping with these feelings.

This is especially important when we experience the emotional impact of patient death. Physicians who lose patients report feelings of self-doubt, failure, guilt and powerlessness. Physicians also report sadness after a patient’s death, including experiencing insomnia and crying.

Traditionally, grief in medical training has been considered weak or unprofessional, and doctors have been encouraged to keep their feelings inside. Rather than openly expressing grief, physicians instead use compartmentalization, isolation and distraction to avoid our negative emotions.

The problem with these techniques is that they are emotional barriers that prevent us from addressing our feelings. Instead, we must practice healthy coping mechanisms such as acknowledging our feelings and accepting support from others.

Share your feelings

Physicians are often reluctant to share our negative emotions with others. Sometimes we choose not to share the negatives in our life because we don’t want to burden our friends or partners. This noble intention can cause a relationship rift because it does not allow others in our life to offer support. Ultimately, that leads to our own isolation. It is critically important to open up about our feelings with those closest to us—a family member or trusted friend or colleague.

In some cases, we may need to reach out to a professional to help us cope with powerful emotions. Asking for help is not a sign of weakness. It takes more courage to ask for help than it does to suffer in silence. And getting help makes us stronger so we can help others.

We must remember that we are not alone. Physicians are incredibly resilient—you do not get through medical school, internship and residency without incredible fortitude. We will get through this as well. We just need a little help from our friends, family, each other and, perhaps, a good psychologist.

Optimizing practice environment, outcomes, and patient satisfaction

Physicians must play a critical role in setting the tone in an ophthalmology facility

By Lynda Charters; Reviewed by Suber S. Huang, MD, MBA

“You MAKE THE weather. Own your outcome. Create the culture.” These are 3 big tasks that Suber S. Huang, MD, MBA, assigned that were perhaps previously unrecognized by ophthalmologists.

There are 3 important ingredients in this recipe, according to Huang, president and CEO, Retina Center of Ohio, voluntary assistant clinical professor, University of Miami, Bascom Palmer Eye Institute.

“The physician has a critical role in developing and leading the professional culture of the organization,” he said. “Collaborative partnering approaches between the physician team and the patient are important in fostering efficient and effective care, and patient satisfaction and retention of patients is the most important metric for financial success and the cornerstone of organizational sustainability.”

CLIMATE CHANGE

Upon entering the office, physician leaders, administrative leaders, and technician leaders must thoroughly believe in what they are doing. These individuals set the tone in the office, which is a major factor in making the office operate more efficiently.

“There is no substitute for leadership, organization, discipline, and the professional will to follow through on a desired plan of action,” Huang said.

If a physician is trying to implement a new office system that will result in more efficiency and productivity and be more helpful to people, that plan must be believable to every person in the office, and the physician must partner with his or her patients, according to Huang.

LEAN AND MEAN

Huang advised physicians to determine what the real goal is from greater office efficiency, such as adopting a lean strategy. Are the goals increased income and/or time savings? But, importantly, what are the effects on each physician, patients, and staff members. “Faster” and “more” are not necessarily better.

According to Huang, physicians must understand that their missions, that which they divined in their heads, is not necessarily everyone’s mission.

“They need to articulate exactly the physician’s vision, the mission, and the best possible outcome,” he said.

Asking everyone from the new technician to the senior partner to describe the perfect day should reflect the same vision as the physician so that the avenue to the goal is clear. Although that perfect outcome may not be readily attainable, redirection can be undertaken, he emphasized. Huang also advised that doing it right the first time is the best route. Time is wasted when a mistake is made and the situation is revisited.

“For example, if endophthalmitis develops in a patient, but the physician performed the surgery 15% faster, he or she is going backward,” he said.

Being lean does not work in a vacuum. Huang explained that everyone in the office is involved in creating an efficient environment.

“The sobering statistic is that 65% to 92% of lean programs fail,” he pointed out.

The reasons for the failures include the following: lack of management support and no idea how to actuate support; incorrect strategy deployment, with the focus on saving seconds versus achieving a better outcome and greater satisfaction for patients; choosing an incorrect project to achieve more efficiency within an individualized environment and not attempting to emulate the unattainable; inappropriate team members, including those who are simply unable to embrace the system; incorrect scope, such as a project that may be too all-encompassing considering all the individuals involved in a large practice; incorrect measurement system; and incorrect implementation.

Huang highlighted 2 important trends of economic forecasting. The first, the broken-arrow era, is defined as the time when physicians are about to be overrun and slaughtered and financial austerity is important.

“The current financial system is in the broken-arrow era,” he said. “Of all the factors that play into the total cost of health care, the rate and unit cost of injections is the fastest-growing health care cost, and it is appropriate to look at.”

The second trend is the concept that as more is learned about how to care for patients, the recognition is that medicine is less art and more protocol, a trend that merits attention, Huang pointed out.

“The trend is between consumer-driven and patient-driven and between physician/patient teaming,” he said. “The patient has to appreciate what the physician is doing, for example, keeping appointment times and delivering perfect health care.”

CREATING THE CULTURE

“The physician has to create a culture that everyone can live with,” Huang said. Patient satisfaction seems to be the key, and many factors drive the patient experience in a practice. A few deserve special attention.

One, as noted in the Accenture Global Customer Satisfaction Report 2008, is that price is not the main reason for customer churn, but rather overall poor quality of customer service.

“A physician may perform examinations faster, but if he or she is perceived as rushing patients through a production line, that patient will not be happy,” he said.

A second observation by Bain & Company, an American management consultancy headquartered in Boston, Massachusetts, is that a customer is 4 times more likely to move to a competitor in the face of a service-related and not a price- or product-related problem.

A related observation by Marketing Metrics is that the probability of selling to an existing customer is 60% to 70% but selling to a new prospect is 5% to 20%.

“This means that your patients are incredibly valuable to your practice,” Huang said. “Physicians must keep their patients happy, and must understand what they fear, what they have, and what they will appreciate.”

Lee Resource reported that for every customer complaint, there are 26 other unhappy customers who have remained silent.

“Physicians must pay attention to even a single complaint,” Huang noted.

In line with this, 1st Financial Training Services reported that 96% of unhappy customers do not complain; however, 91% of those who will simply leave and never return. In support of this, the White House Office of Consumer Affairs found that a customer who is dissatisfied will relate their dissatisfaction to 9 to 15 patients; about 13% of dissatisfied customers tell more than 20 people.

“It makes sense to keep patients happy. As the practices are becoming more efficient, they should not trade off decades of good will,” he said.

The White House Office of Consumer Affairs also reported another interesting statistic, namely, that patients who have their issue resolved will relate that to 4 to 6 people; 70% of buying experiences are based on how the customer feels they are being treated, according to McKinsey. The ideal scenario is avoidance of negative experience, because 12 subsequent positive experiences are needed to make up for that 1 bad experience. Emmet Murphy and Mark Murphy pointed out that a 2% increase in customers has the same effect as decreasing cost by 10%, which is a profound effect on the bottom line.

“There is almost nothing we can do to increase our bottom line by 10%; making sure our patients are happy accomplishes that,” Huang pointed out.
Navigating US immigration in the time of the coronavirus

Future entry into country for graduate medical students, research fellows at risk

By Lynda Charters; Reviewed by Fasika Woreta, MD, and Sidra Zafar, MD

PRESIDENT DONALD TRUMP recently signed an executive order temporarily suspending immigration into the United States in response to the coronavirus pandemic and the need to protect domestic jobs.

The executive order initially was supposed to be in effect for 60 days. However, shortly thereafter the suspension was redefined as indefinite.

This ban raised a question about the ability of foreign medical graduates to enter the country in the next wave of openings for residencies and research positions. Will the new students and fellows be able to come in, and will the ones who are already here be allowed to stay?

According to Fasika Woreta, MD, currently a post-doctoral research fellow at Johns Hopkins University School of Medicine, Baltimore, this is a stressful situation because it is unknown if visas will arrive in a timely fashion.

“There are numerous international graduate students working in many hospitals in the United States, and a travel ban is really going to affect delivery of health care and residency programs throughout the country,” Woreta said. “In addition to affecting clinical care, this ban also affects the ability of research fellows to enter the country. Innovation and research are also important in our mission.”

WHAT TO EXPECT

The Wilmer Eye Institute accepts 5 residents per year. One such student is Dr. Woreta’s incoming resident, Sidra Zafar, MD, who is here on a J1 research visa, but hopes to change to clinical status for a residency slot at St. Agnes Hospital, Baltimore, beginning July 1. This change requires processing of a new visa application in order to begin clinical care. This visa will likely be processed in time, but Woreta foresees a problem securing a visa by students who are currently outside the United States. This ban will change the future of medical education, Woreta pointed out.

“Previously, we were able to rank applicants based on merit and not worry about their visa status,” she said. “If they were exceptionally talented, we would take them at Wilmer. Foreign medical graduates have contributed a lot to the health care system in this country, bringing incredible experience to the table. With suspension of immigration, we will have no choice but to stop accepting these talented students.”

This suspension will have a negative effect on people who live in areas that lack sufficient medical services. “International medical graduates often practice in underserved areas and provide care in places there are shortages of primary-care physicians and psychiatrists. These underserved areas will be affected disproportionately by this suspension,” Woreta explained.

Physicians from all specialties are being deployed to work in intensive care settings. The suspension of immigration will further exacerbate the shortage of qualified internal medicine doctors which will be disastrous during this pandemic, she explained further.

“A temporary or permanent ban on immigration will have dire consequences in hospitals throughout the U.S.,” Dr. Woreta stated.

TIMING IS EVERYTHING

Zafar has been a research fellow for 2 years and matched at the Wilmer Institute for ophthalmology residency, which she will begin in 2021. She currently is on a J1 research visa and is uncertain about the next visa. Her current work visa will expire at the end of June and she is due to start her required 1-year preliminary internship at St. Agnes Hospital on July 1, 2020. Zafar said she is hopeful about obtaining her visa, despite the entire application process being slowed down.

“I have heard however that other individuals at different hospitals are beginning to be approved,” she said. “The current situation seems to be better than it was 1 month ago.”

For Zafar, one option is to extend her current work permit at Johns Hopkins, but she was uncertain if this would result in other problems in the processing of her visa. Returning to her home country of Pakistan is not possible because all airports are closed and she would not be able to return to the United States anytime soon.

The medical students coming from Pakistan, who would be entering the United States on a J1 visa are at the mercy of the COVID-19 virus because all flights have been suspended. In addition, all of the graduate medical students require a Statement of Need from the Minister of Health in Pakistan issued by the U.S. Educational Commission for Foreign Medical Graduates. Because of the pandemic, obtaining these statements has become increasingly difficult.

“I am in a state of apprehension because there is such great uncertainty about what is going to happen,” Zafar concluded. “However, I am hoping for the best and that I will be able to start my residency training on time. At the end of the day, the international medical graduates contribute greatly to healthcare in the United States.”

REFERENCE


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Dr Huang has no financial interest in any aspect of this report.
Subretinal gene therapy safe with visual benefit

Study finds use in achromatopsia may revitalize cone photoreceptors

By Lynda Charters; Reviewed by M. Dominik Fischer, MD, PhD

A gene therapy treatment may hold promise for treating an inherited ocular disease, achromatopsia, after a study found it provided some visual improvements in treated patients.

The disease, for which there is no current treatment, affects the retinal cone receptors, and is characterized by day blindness, glare, poor vision, nystagmus, and partial or total absence of color vision. Affected patients have no cone response from birth, which is in contrast to the more common types of color blindness that result from changes in the opsin genes that only impact patients’ efficiency with which they detect light frequency or wavelength, according to M. Dominik Fischer, MD, PhD.

Fischer is professor of ophthalmology at the Oxford University Hospitals NHS Foundation Trust, Oxford, UK and at the Centre for Ophthalmology, Eberhard Karls Universität Tübingen, Tübingen, Germany, and lead author of the study.

“Members of the RD-CURE consortium have started to look into achromatopsia already 25 years ago, identifying its genetic basis and developing treatment options,” he said.

Achromatopsia had previously been considered to be nonprogressive; however, recent research has identified structural changes with increasing age that investigators found to be consistent with slowly progressive deterioration and loss of the cone photoreceptor cells. Ninety percent of cases are associated with variants in 6 genes, and the most prevalent of these variants are in 2 genes, he explained, that encode the α and β subunits of the cone cyclic nucleotide-gated channel, CNGA3 and CNGB3. The former occurs in from 25% to 28% of cases in Europe and the United States and the latter in half of cases.

“The CNG channels are essential components of the phototransduction process in cone photoreceptors, which enable daylight vision, high spatial and temporal resolution, color discrimination, and stable fixation,” Fischer said.

Fischer and his colleagues conducted an open-label exploratory, nonrandomized, controlled trial to determine the safety and efficacy achieved with one subretinal injection of gene vector therapy adeno-associated virus CNGA3. Three doses of the therapy were tested, $1.0 \times 10^{10}$ vector genomes (vg), $5.0 \times 10^{10}$ vg, and $1.0 \times 10^{11}$ vg. Three patients each received one of the doses. The study patients, all of whom had confirmed achromatopsia and variants in CNGA3, then were followed for 12 months. The primary outcome was safety and the secondary outcomes were changes in visual function, including spatial and temporal resolution and chromatic, luminance, and contrast sensitivity over the 12 months of the study.

**RESULTS**

The study included 9 patients (8 men, 1 woman; mean age, 39.6 years). The surgeries were performed with no complications; no substantial safety issues arose during the follow-up period.

The investigators reported, “despite the congenital deprivation of cone photoreceptor-mediated vision in achromatopsia, all 9 treated eyes demonstrated some level of improvement in secondary end points regarding cone function, including mean change in visual acuity of 2.9 letters. Contrast sensitivity improved by a mean of 0.33 log.”

“This study provided clinical proof of concept for viral vector-mediated gene supplementation therapy of inherited day blindness caused by pathogenic variants in the cone photoreceptor-specific gene CNGA3. While all applied dose levels showed some benefit, we will continue with the highest tolerated dose in a phase IIb trial,” Fischer said.

This next investigator-led trial looks at the feasibility of earlier treatment in patients who are about 7 to 8 years of age to determine whether earlier intervention will provide greater benefit. ■
Minimally invasive glaucoma shunt delivers for patients

Another option for ophthalmologists, gelatin stent is found to lower pressure

By Steve Lentier; Reviewed by Hari Jayaram, MD, PhD

The first minimally invasive glaucoma shunt was developed by AqueSys, which led to the company’s acquisition by Allergan in 2015. Not long after, the product was launched in Europe as the Xen transscleral gelatin stent.

The Xen stent is a 6-mm long hydrophilic gelatin stent, with an inner diameter of 45 micrometers. It is inserted with a preloaded injector, through a corneal incision, and exits into the subconjunctival space to form a bleb. Usually, mitomycin C is injected prior to stent insertion.

The insertion can be performed as a standalone procedure or combined with cataract surgery. In the United States, Xen is licensed as a treatment for refractory glaucoma in cases where previous glaucoma surgery may have failed or in cases that have become nonresponsive to maximum tolerated medical therapy. In Europe, however, the stent was launched for use as a primary surgical intervention that may prevent or delay the need for trabeculectomy and that can be performed at the same time as cataract surgery.

Hari Jayaram, MD, PhD, of the Glaucoma Service at Moorfields Eye Hospital in London, recently presented the results of a study of 7 years of data on surgical experience at Moorfields. The majority of the cases were of the second type mentioned above, as a primary intervention, which indicates that Xen is suited to primary open-angle glaucoma (POAG) when drops are not enough or previous medical treatments have failed.

STUDY DESIGN

The investigators performed a retrospective review of all ab-interno Xen procedures that had been performed at Moorfields. In extracting the data, they paid special attention to the patient’s ethnic origin and primary underlying diagnosis, their IOP and medication history over the time of follow-up, whether or not the patient required further glaucoma surgery. They also looked at the incidence of complications, in particular hypotony and infection, as well as loss of vision.

Failure was determined using a generous composite outcome, including an IOP definition of less than 20% reduction of IOP from the highest recorded pressure in the patient’s medical record, either with or without the use of eye drops. Outcomes measured included whether or not a patient was using drops, and failure also included reoperation for glaucoma, endophthalmitis, or loss of light perception vision. Importantly, the need for bleb needling was not included among the criteria for failure.

The study looked at Xen insertions performed at Moorfields from May 2012 to June 2019. This included a total of 426 eyes from 375 patients. Five percent of the patients had undergone prior surgery for glaucoma. Almost two-thirds of the patients had an underlying diagnosis of POAG, and about a quarter had an underlying diagnosis of either uveitic glaucoma or another form of secondary open-angle glaucoma.

There was a wide age range of patients receiving the stents, from 16 to 95 years, with a mean age of 67. The patient population was typical of the ethnic diversity seen in London, with around 44% of patients coming from nonwhite British ancestry.

Sixty percent of the cases were performed as standalone procedures and 40% were combined with cataract surgery. Mitomycin C was used almost universally. Some surgeons also used anti-VEGF treatments, and long-acting corticosteroid therapies.

RESULTS

The graph at left shows the long-term outcomes, using the above-mentioned definition for failure. At 1 year, 64% of the procedures were found to be successful. This reduced to 41% after 4 years. One interesting thing noted by the investigators is that almost a third of patients failed within the first postoperative year.

Comparing standalone to combined surgeries showed no significant difference in the survival curve of the 2 groups. The researchers also looked at the impact of ethnicity. Patients of nonwhite British ancestry showed no significant difference in the survival curve of the 2 groups.

SURGICAL SUCCESS RATES:

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(Chart courtesy of Hari Jayaram, MD, PhD)
Amid pandemic, FDA takes aim at fraudulent medical products
The agency is targeting scam artists on internet as pace of research steps up

By David Hutton

THE FDA IS taking a stand against companies attempting to profit off the COVID-19 pandemic through fraudulent medical products as it increases emergency use authorization for certain medical devices.

From research and development of new devices for COVID-19 to seeking out fraudulent claims, the FDA has been faced with myriad issues during this pandemic.

FDA Commissioner Stephen M. Hahn, MD, in prepared remarks, said the agency has reviewed and issued emergency use authorizations for medical devices for COVID-19 at a fast pace.

“There was a special focus on the development and availability of accurate and reliable COVID-19 tests,” Hahn said. “We need to know who has the disease and who has had it. This is essential if we are to understand this virus and return to a more normal lifestyle.”

Hahn also pointed out that drug research is being conducted at a record pace.

“More than 90 drugs are being studied, and FDA is actively working with numerous vaccine sponsors, including three sponsors who have announced they have vaccine candidates that are now in clinical trials in the U.S.,” he said. “More than 144 clinical trials have been initiated for therapeutic agents, with hundreds more in the pipeline. We do not have a cure or vaccine yet, but we’re on our way, at unprecedented speed.”

In a statement, the FDA announced it is taking several steps to find and stop scam artists on the internet selling unproven medical products that fraudulently claim to mitigate, prevent, treat, diagnose, or cure COVID-19.

“While we seek to ensure access to critical medical products, it is imperative that we continue our efforts to find and prevent the sale and distribution of products that may be harmful to the public health,” said FDA Associate Commissioner for Regulatory Affairs Judy McMeekin, PharmD, in the release. “Americans can rest assured that we’re leveraging our experience investigating, examining, and reviewing medical products, both at the border and within domestic commerce, to help ensure that the critical resources reaching the front lines in the battle against COVID-19 are appropriate.”

McMeekin said the FDA takes its responsibility seriously to determine whether the medical products coming into our country are fraudulent, counterfeit or illegitimate, and it takes action as needed.

The agency has already issued 42 warning letters to companies marketing the fraudulent COVID-19 claim.

Through the FDA’s Operation Quack Hack, the agency has identified hundreds of such bogus products including fraudulent drugs, testing kits, and personal protective equipment being sold online with unproven claims. The FDA is working with partners in the technology sector to remove these products from their platforms, the release says.

Anyone aware of these fraudulent devices is asked to report them to the FDA.

A recent case where mislabeled COVID-19 “treatment kits” were offered for import led to a criminal complaint being filed with the U.S. Justice Department against a British man who sought to profit from the pandemic and jeopardize public health, according to the release.

STENT

(Continued from page 30)

in keeping with the understanding that there is a more aggressive wound healing response in these ethnic groups. However, when successful, and further surgery was not required, patients with the Xen achieved a mean IOP of around 15 mm Hg.

MEDICATION REDUCTION

There was a mean reduction in medication use from 3 drops prior to surgery to about 1.3 drops over long-term follow-up in patients classified as successes. In terms of achieving drop independence, about 40% of patients who did not require further glaucoma surgery were drop free beyond a 2-year period.

C O M P L I C A T I O N S

Hypotony occurred in about 1 in 5 patients but responded well to conservative management.

There was only 1 case of cleft formation that required surgical intervention. Bleb needling was very common, with 26% of patients needing at least 1 bleb needling procedure within the first 3 months after surgery.

The need for further surgery was the cause of failure in around a third of patients. Over half of these were revision procedures, which tended to be necessary early on in the postoperative course with a median time to reoperation of 4 months.

INFECTION RATE

The overall infection rate was 1.6%. This is lower than that reported in the trabeculectomy group in the Tube Versus Trabeculectomy (TVT) Study (NCT00306852), which was 1.9%. However, it is higher than for all ocular surgery at Moorfields performed in 2018 (0.02%) and higher than the infection rate (0.3%) derived from annual core trabeculectomy outcome audits performed at the hospital.

C O N C L U S I O N

The authors concluded that when stent insertion is successful, and further revision surgery is not required, the Xen stent can effectively lower pressure and reduce the need for medications. They noted, however, that surgeons should be aware of potentially high rates of reoperation and the long-term risks of bleb-related infection, and said that refining surgical technique and careful patient selection in the future may help optimize outcomes.

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Dr Jayaram has no financial disclosures related to this content.
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