Conjunctival Melanoma
Unlocking Mysteries of Disease

Directed targeted therapies and even drugs that can retrain the immune system are being developed for these patients.

By Lynda Charters; Reviewed by Uday Devgan, MD

Not much is known about conjunctival melanoma aside from the fact that it is rare and develops in about 0.5 persons/million among Caucasian patients. The etiology is unknown, but it occurs in individuals with lighter complexions. The importance of exposure to sunlight also remains unknown.

What is known is that it recurs in from 5% to 26% of cases, spreads with regional lymph node metastasis in from 15% to 40% of cases and systemic metastasis in from 9% to 25%, and it kills, with 10-year mortality rates ranging from 9% to 30%, according to Sara E. Lally, MD, who spoke at the 2019 meeting of the American Academy of Ophthalmology.

Studies of conjunctival melanoma have implicated a number of mutations, including the BRAF, NRAS, NF1, and TERT mutations, she noted, but questioned why researchers are concerned with them.

"Previously, when patients developed metastatic diseases, they underwent chemotherapy that wiped out the entire system. Now, directed targeted therapies and even drugs that can retrain the immune system are being developed for these patients.

LBS-008, a novel therapy for Stargardt disease and dry age-related macular degeneration (AMD), has a big job with big promise. It is the first oral drug for treating dry AMD and Stargardt disease, which until now have not been treatable and are blinding disorders.

LBS-008 (Bellite Bio) is a nonretinoid antagonist of retinol binding protein 4 (RBP4).

The drug partially inhibits the uptake of serum retinol from circulation to the retina and partially reduces the concentration of the visual cycle retinoids and then inhibits the biosynthesis of cytotoxic bisretinoids in the retina. LBS-008 prevents the accumulation of the toxins that contribute to pathogenesis of these two diseases, said Konstantin Petrukhin, PhD, at the 2019 meeting of the American Academy of Ophthalmology.

Continues on page 21: Stargardt

Issue Highlights

Clinical Diagnosis
Casting a net to diagnose, treat conjunctival lymphoproliferative lesions

Surgery
Prospective evaluation highlights performance of trifocal toric IOL

Therapeutics
Researchers investigating union between MIGS, medication

Imaging
Best anterior-segment imaging for corneal transplants

Device Technology
IOL power calculations gaining accuracy

Gene Therapy
Research targeting precision dosing for gene, cell therapy

OphthalmologyTimes.com
The first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis

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

- Cenegermin-bkbj, the active ingredient in OXERVATE, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues.

- NGF is an endogenous protein involved in the differentiation and maintenance of neurons, and acts through specific high-affinity (ie, TrkA) and low-affinity (ie, p75NTR) NGF receptors in the anterior segment of the eye to support corneal innervation and integrity. Endogenous NGF is believed to support corneal integrity through 3 primary mechanisms (shown in preclinical models): corneal innervation, reflex tear secretion, and corneal epithelial cell proliferation and differentiation

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

Important Safety Information

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

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

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

Explore the breakthrough therapy at Oxervate.com/HCP

*Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment. Based on results from the REPAIR trial (Europe, N=212; N=156) and the US trial (N=44);18

Brief Summary of Safety
Consult the full Prescribing Information for complete product information.

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

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

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

ADVERSE REACTIONS
Clinical Studies Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

**13 Technique Puts Focus on Presbyopia Laser Correction**
Procedure has achieved stable depth of focus and micro-monovision.

**17 Database IDs Risk Factors for Iris Damage, Dropped Nucleus**
The European Registry for Quality Outcomes in Cataract and Refractive Surgery builds database.

**18 Light Trial Focuses on Lowering IOP, Keeping It There**
Repeat-SLT lowers IOP in eyes in which pressure increased after first application.

### Therapeutics

**19 Dexamethasone Insert Reduces Postsurgery Burden**
Device may reduce or eliminate need for corticosteroid drops after cataract surgery.

**20 Are Topical Antibiotics Needed After Cataract Surgery? Maybe**
While topical antibiotics are not needed after routine surgery, intracameral antibiotics must be used.

### Device Technology

**22 Module Bridges Remove Gap in Learning, Mentorships**
Platform links health personnel in developing countries to healthcare experts worldwide.

**23 Heads-Up Brings Ergonomics to Cataract Surgery**
Technology proves to offer safety, efficiency that is similar to traditional approach.

**24 AI-Enabled Tool Offers Glimpse of Glaucoma-Related Functional Loss**
Researchers create a tool for assessing visual function in patients with glaucoma.

### Imaging

**29 OCT Useful in Hands of Anterior Segment Specialists**
Anterior-segment OCT systems vary in scanning width, depth, and resolution.

**30 Mild Traumatic Brain Injury Affects Visual, Neurocognitive Function**
Eye movement dysfunction is one consequence of mild traumatic brain injuries in pediatric patients.

### Clinical Diagnosis

**32 Keys to Assessing True Crosslinking Outcomes**
Virtual Bowman’s topography software provides a new noninvasive way to look at crosslinking outcomes.

**33 Diagnostic Advances Offer Glimpse of Endophthalmitis Pathogens**
Molecular diagnostic techniques offer improved sensitivity for detecting pathogenic organisms in postoperative endophthalmitis.

### Gene Therapy

**26 Study Targets Subretinal Option for AMD Treatment**
RGX-134 gene therapy delivered subretinally shows dose-dependent sustained improved vision.

**27 Examining the Long and Winding Road of Gene Therapy**
Retinal gene therapy is making a move from science fiction to science fact.
Thanksgiving food for thought

Mike Hennessy Sr., Chairman and founder of Ophthalmology Times’ parent company, MIH Life Sciences

NOVEMBER IS A TIME for giving thanks, and with new tools and techniques, there is plenty for ophthalmologists to be thankful for. All of this means that physicians can provide better results for their patients in a more efficient and effective manner.

On the cover of this issue of Ophthalmology Times, we examine an oral therapy that targets Stargardt disease and age-related macular degeneration (AMD). Konstantin Petrukhin, PhD, discusses LBS-008, the first oral drug for treating dry AMD and Stargardt disease, which, until now, have not been treatable and are blinding disorders.

Our therapeutics coverage continues inside with a look at the dexamethasone insert, which offers a lower treatment burden after cataract surgery. John A. Hovanessian, MD, tells us that it reduces the pain and inflammation after cataract surgery in the second eye to a level that is comparable to pain in the first eye that underwent cataract surgery. Alexander James Silvester, MBCHB, and Anil Pitalia, MBCHB, tell us how topical antibiotics are unnecessary after routine cataract surgery, but intracameral antibiotics must be used to prevent endophthalmitis.

Also on the cover, we examine conjunctival melanoma, a disease that remains a mystery of sorts. Sara Lally, MD, provides insight that helps us unravel some of that mystery.

We continue our clinical diagnosis coverage with Gairik Kundu, MBBS, MS, who discusses some of the keys to assessing true crosslinking outcomes. He notes that a novel method of noninvasively evaluating the outcomes after crosslinking is under development.

In surgery, Michiel H.A. Luger, MD discusses his research, performing PresbyMAX hybrid presbyopia laser correction, which is a micro-monovision technique plus an asymmetric extended-depth-of-focus approach, by induction of negative spherical aberration. This technique achieved stable extended depth of focus and micro-monovision. High patient satisfaction was achieved in overall visual quality and visual performance over the long term.

Data can be an invaluable tool during surgery, and Mats H. Lundstrum, MD, discusses with us the European Registry for Quality Outcomes in Cataract and Refractive Surgery, which has amassed an enormous data that identifies risk factors for cataract surgery patients. Our surgery coverage this month also includes look at the LIGHT Trial, which is examining ways to lower IOP and keep it low.

We also can be thankful for the latest developments in device technology. One example highlighted in this issue is the Cybersight platform from Orbis International, which links health personnel in developing countries to health-care experts worldwide for consultations and training. Siama Yousefi, PhD, explains how researchers have been able to use artificial intelligence to create a new tool for assessing the visual function of patients with glaucoma designed to overcome the limitations of existing algorithms.

Rounding out our device technology content is a look at heads-up cataract surgery, which can help surgeons work more effectively and efficiently. But is it the future? Robert J. Weinstock, MD, details the findings of a retrospective study that offers some insight.

We are seeing some interesting developments in gene therapy, including RGX-314, a treatment for wet AMD delivered subretinally. In clinical studies, it has demonstrated dose-dependent sustained/improved vision and a good safety profile. Jeffrey Heier, MD, discusses research on this gene therapy, a proprietary gene delivery platform that is believed to deliver longer and higher protein expression with a lower immune response that earlier generation adenoviral based viruses used for gene therapy.

Imaging is providing some interesting food for thought this Thanksgiving season. Mild traumatic brain injury can impact visual and neurocognitive function. Eye movement dysfunction is one consequence of mild traumatic brain injury in pediatric patients. Mitchell B. Strominger, MD, discusses emerging data from studies using functional magnetic resonance imaging to show new information about neurocognitive impairment.
The problem with patient reviews
Online reviews can make or break a physician

The reviewers say very negative things, claiming that the doctor “waters down the Botox,” delivers less product than the customer paid for, or delivers poor outcomes—“my face looks worse than before.” The doctor’s complaint says the reviews are “knowingly and materially false.”

Dr. Mirza says unregulated and anonymous speech on social media does not serve the interests of society. “These platforms need to be regulated in the same way we regulate other industries. Reviewers can’t just hide behind the screen.”

According to the article, Dr. Mirza has previously sued negative reviewers and prevailed in court. Earlier this year, two reviewers were prohibited from posting online comments and had to remove their posts about his practice.

Eighteen months ago, he sued Yelp in order to obtain the identities of the reviewers he is currently suing. The article points out that a federal court in Virginia ruled in 2014 that “anonymous users are not protected by the First Amendment if the review is based on false statements.”

How will it play out?
It will be interesting to see how cases like this play out in court. Complaining about doctor visits is a time-honored tradition in our country (“Why are magazines in the waiting room so old?”), but what is the obligation of someone complaining online to be truthful and accurate about their doctor?

For most physicians, suing patients is simply something we don’t do. Rather, people sue us. Will that change if physicians feel that they are the victims of untrue and malicious critiques by anonymous posters?

Comedian Dave Chappelle recently spoke to the issue of free speech and the anger it sometimes causes: “The First Amendment is first for a reason. Second Amendment is just in case the first one doesn’t work out.”

References

- https://www.medpagetoday.com/publichealthpolicy/generalfederalissues/83133
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

**Indication**

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

**Important Safety Information**

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

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

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

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration. Safety and efficacy in pediatric patients below the age of 17 years have not been established.

**Check out Xiidra-ECP.com**

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

References:

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

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

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

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

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

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

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

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

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

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

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

**NONCLINICAL TOXICOLOGY**
**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. Mutagenesis: Lifitegrast was not mutagenic in the in vitro Ames assay. Lifitegrast was not clastogenic in the in vivo mouse micronucleus assay. In an in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

**Impairment of fertility:** Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD]) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421. For more information, go to www.Xiidra.com or call 1-800-828-2088. Marks designated ® and ™ are owned by Shire or an affiliated company. ©2018 Shire US Inc. SHIRE and the Shire Logo are trademarks or registered trademarks of Shire Pharmaceuticals Inc. or its affiliates. Patented: please see https://www.shire.com/legal-notice/product-patents Last Modified: 01/2018 S33769
Hypersonic vitrectomy is a new method of removing the vitreous in which ultrasonic power is used to actuate the vitrectomy probe. Thus far, this technology has been used in more than 200 cases performed by 17 surgeons to treat myriad vitreoretinal pathologies, according to Carl C. Awh, MD.

He highlighted cases in which a 23-gauge hypersonic vitrectomy probe was able to quickly remove thick, chronic vitreous hemorrhage resulting from proliferative diabetic retinopathy; to fragment and remove an entire dislocated dense nucleus; and to aspirate 1,000 centistoke silicone oil from the vitreous cavity. This display may raise the question about whether it is now time to replace the tried-and-true guillotine cutter.

Though hypersonic vitrectomy has proven to be excellent in most situations and has expanded capabilities—such as the ability to perform lensectomy and remove silicone oil—it is not always the equal of current guillotine cutters, said Dr. Awh, president of Tennessee Retina, Nashville, TN.

“I find that, in some cases, it does not work as well as my guillotine cutter,” said Dr. Awh, noting that the device sometimes seems to have suboptimal cutting power.

As an example, he described a phenomenon of what he calls “stranding,” when strands of native collagen are revealed during hypersonic vitrectomy. These strands are eventually severed by the hypersonic vitrectomy probe. There seems to be no peripheral traction created and no iatrogenic breaks created, but the appearance of the strands is disconcerting, he noted. Dr. Awh said he would prefer that the hypersonic cutter cut them more effectively.

Similarly, he has observed that while the hypersonic probe can cut fibrovascular membranes, it does not always accomplish this task as efficiently as a guillotine cutter. Despite these reservations, Dr. Awh predicts significant improvements in the performance of hypersonic vitrectomy.

FLUIDICS OF VITRECTOMY

Dr. Awh discussed recent observations about the fluidics of vitrectomy. Ultra-high-speed video demonstrates that even a hypersonic vitrectomy probe with a constantly open port does not have completely uninterrupted inflow. Although there is net inflow, longitudinal oscillations of the probe and the inertial lag of the fluid column within the lumen of the probe result in the egress of a tiny amount of fluid during the “upstroke” of the hypersonic probe.

This effect is best visualized in a fluid medium and when no active vacuum is being applied. This effect is not visible during vitrectomy due to the dampening effect of vitreous and to the net ingress of vitreous and fluid when active vacuum is applied.

However, this effect is one of the main reasons that ultra-high-speed video demonstrates turbulence at the tip of the probe. This turbulence is present with all types of vitrectomy cutters and is greater with guillotine cutters.

With the hypersonic vitrectomy probe, a reduction in gauge size and changes in port geometry can reduce turbulence, which should result in cutters with more predictable and stable fluidics.

HANDPIECE MODIFICATIONS

Cases performed to date with hypersonic vitrectomy have been with a device operating at a frequency of 31 kHz, or 1.8 million “cuts” per minute, he noted. The next-generation device will operate at frequencies up to 41 kHz with an increase to 2.5 million cuts per minute.

The increased frequency will result in increased flow, but Dr. Awh points out that this will not be the most valuable difference.

“Shear stress, that is, cutting power, increases in a quadratic relationship to frequency, such that increased frequency equals increased cutting power and increased flow,” he said.

The downside to taking two steps forward is the one step back due to increased turbulence that may result from increased frequency.

To address this concern, the next-generation device will incorporate adaptive frequency control to adjust the frequency instantaneously in response to changes in tissue behavior.

“Hypersonic vitrectomy has the potential to provide performance superior to current state-of-the-art guillotine vitreoretinal cutters,” Dr. Awh concluded.
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DAVS viewing system yields increased sense of situational awareness

By Lynda Charters; Reviewed by John D. Pitcher III, MD

3-D DIGITALLY ASSISTED vitreoretinal surgery (DAVS) is an alternative viewing system from the conventional operating microscope that includes some high-tech features: a 3-D high-definition dynamic-range camera, ultra-high-speed low-latency processor, 3-D 4K surgical display, and passive polarized 3-D glasses.

Two such systems are currently commercially available, the Zeiss ARTEVO 800 System and the Alcon NGENUITY System, according to John Pitcher III, MD, a retina surgeon at Eye Associates of New Mexico and assistant clinical professor, University of New Mexico, Albuquerque, NM.

THE DAVS ADVANTAGE

DAVS seems to have checked all the boxes on the surgeons’ wish list, with upgrades in visualization, augmented reality, and safety.

DAVS provides visualization that is enhanced in three areas: 42% better depth resolution, 48% more magnification, and 5x extended depth of field, Dr. Pitcher stated.

‘This real-time data allows the surgeon to adjust the surgical technique or steps to provide the best outcome for the patient.’

— John D. Pitcher III, MD

When it comes to augmented reality, the filters in the DAVS system provide enhanced visualization. Surgeons have the ability to select, for example, a green-free filter that allows visualization of indocyanine green on the macula to more clearly identify the internal limiting membrane.

A second feature, image overlay, is now available in retina surgery and facilitates a view of all data that the surgeon would need intraoperatively at his or her command. Dr. Pitcher explained that the screen provides the infusion pressure in the upper left, vacuum upper right, cut rate lower right, and inversion of the screen center top.

“This technology lets the surgeon know that without looking away from the screen that a higher cut rate, lower vacuum setting is operating and provides better safety for shaving in the peripheral retina,” he said.

Dr. Pitcher demonstrated that during an air/fluid exchange, the image overlay technology shows on the upper left the switch from air to infusion pressure with balanced salt solution and the laser settings with the number of spots delivered in the lower right of the screen.

“This technology allows the surgeon to have all of this information in a heightened sense of situational awareness without looking away from the patient,” Dr. Pitcher emphasized.

Another feature of augmented reality is the integration of optical coherence tomography into surgery.

“This allows, for example, visualization of a full-thickness macular hole on horizontal and vertical B-scans,” Dr. Pitcher explained.

Surgeons also can see the posterior hyaloid face, macular traction, or any epiretinal remnants that remained unpeeled.

“This real-time data allows the surgeon to adjust the surgical technique or steps to provide the best outcome for the patient,” he said.

A key concern for surgeons is safety. Reduced lighting intraoperatively is needed in some settings to enhance visualization and safety. Reduction of the light source to 10% of potential still allowed good results during membrane peeling. Reduced light decreases the possibility of phototoxicity to the retina.

A second safety feature is that surgical efficiency may increase with the use of a head-up display compared with use of the standard microscopic view. The membrane peeling time was shown to decrease significantly with the head-up display.

As with all new technologies, a learning curve exists and the desired surgical integration of DAVS may be completed over time.

JOHN D. PITCHER III, MD
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Dr. Pitcher reported receiving research funding from Alcon.
In 2012, a research team led by Michiel H.A. Luger, MD, conducted a study performing PresbyMAX hybrid presbyopia laser correction, which is a micro-monovision technique plus an asymmetric extended-depth-of-focus approach, by induction of negative spherical aberration (SA).

In the distance eye, they targeted emmetropia and added a low negative SA. In the near eye, the team targeted a low myopia (-0.9 D), and added more negative SA, in order to achieve different depths of focus in the distance and near eyes.

In the study, the researchers employed the Near Activity Visual Quality Questionnaire (NAVQ) and the Quality of Vision (QoV) questionnaire both preop and postop. They also studied contrast sensitivity and glare, corneal aberrations, and ocular aberrations. Treatments were performed with Intralase iFS and AMARIS 750S.

RESULTS AFTER SIX YEARS
The one-year results were published in the American Journal of Ophthalmology,1 and were quite good. But in order to know if the results were lasting long term, the group recently recalled the entire cohort to follow up after a six-year interval. Of the original 32 patients, 19 (60%) agreed to be included again, and these 38 presbyopic eyes were followed longitudinally.

UNCORRECTED DISTANCE VISUAL ACUITY
At six years post-op, the uncorrected distance visual acuity appeared to be quite stable over time, especially binocularly, with a trend for slight improvement in the near eye.

QUALITY OF VISION
Surprisingly, quality of vision improved over time. Initially there were issues with hazy vision, blurred vision, or double vision, which the authors believe had to do with adaptation and differences in depth of field, but over time it completely resolved and was even slightly improved (not significantly) over baseline.

REFRACTIVE ASTIGMATISM/KERATOMETRY/SPHERICAL EQUIVALENT
Refractive astigmatism and keratometry were stable, but there was some progress in spherical equivalent. This is due to lenticular changes and presbyopia progression of 0.12 D per year, which is in line with the literature.

DISTANCE VISUAL ACUITY
For distance visual acuity, the team achieved 20/20 binocular in 73% of patients, and quality of vision was comparable to before the operation. The initial effects of night vision symptoms decreased over time, and there was a good refractive outcome in that there was separation between the distance eye and near eye, and stability was achieved almost instantaneously.

Looking again at the NAVQ questionnaire there were a few items that were not as good after one year as they were pre-operatively, but all ten items resolved and became significantly better than they had been at baseline.

UNCORRECTED NEAR VISUAL ACUITY
Uncorrected near visual acuity was better than J2 binocularly, and J3 was achieved in over 75% of patients. Answers on the NAVQ questionnaire improved from little satisfaction to high satisfaction on all questions, although decreased from a one-year follow-up.

DISTANCE CORRECTED NEAR VISUAL ACUITY
For distance corrected near visual acuity is stable. There is some progression, due to presbyopia progression. Defocus curves also show some presbyopia progression which is in line with the current literature.

MULTIFOCALITY
Distance corrected visual acuity is at the level of J6 in over 75% of patients. The defocus curves show no loss in best focus, no change for intermediate vergences, and a mean gain of one line for near vergences. This is a little worse than at one-year follow up.

Researchers examine long-term results of hybrid approach for patient satisfaction

By Steve Lenier; Reviewed by Michiel H.A. Luger, MD

Dr. Luger

AMARIS 750S.

RESULTS AFTER SIX YEARS
The one-year results were published in the American Journal of Ophthalmology,1 and were quite good. But in order to know if the results were lasting long term, the group recently recalled the entire cohort to follow up after a six-year interval. Of the original 32 patients, 19 (60%) agreed to be included again, and these 38 presbyopic eyes were followed longitudinally.

Data courtesy of Michiel H.A. Luger, MD.

PRE-OP (2012)

<table>
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<td>J4</td>
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</table>

6 Y follow up interval

N = 19 patients (38 eyes) out of original 32 patients (64 eyes) (60%)
START WITH
THE POWER OF EYLEA

AS DEMONSTRATED IN PHASE 3 CLINICAL TRIALS¹

INDICATIONS AND IMPORTANT SAFETY INFORMATION
EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

CONTRAINDICATIONS
• EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

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

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON
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777 Old Saw Mill River Road, Tarrytown, NY 10591
**ADVERSE REACTIONS**

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

*Please see Brief Summary of Prescribing Information on the following page.*

anti-VEGF = anti–vascular endothelial growth factor; AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; MEfRVO = Macular Edema following Retinal Vein Occlusion.

**References:**
BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on MCKPortal US for additional product information.

1 INDICTIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

2 CONTRAINDICATIONS
- Hypersensitivity
- Endophthalmitis and Retinal Detachments
- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [see Adverse Reactions (6.1)].

3 WARNINGS AND PRECAUTIONS
- Endophthalmitis and Retinal Detachments [see Warnings and Precautions (5.1)].
- Hypersensitivity [see Adverse Reactions (6.1)]
- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachment [see Adverse Reactions (6.1)].

5 ADVERSE REACTIONS
- The following potentially serious adverse reactions are described elsewhere in the labeling:
  - Hypersensitivity [see Adverse Reactions (6.1)].
  - Endophthalmitis and retinal detachments [see Warnings and Precautions (5.1)].
  - Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachment [see Adverse Reactions (6.1)].

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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.
- A total of 2905 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2359 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients treated with EYLEA were conjunctival hyperemia, eye pain, vitreous detachment, vitreous floaters, and intracocular pressure increases.

6.2 Animal Data
- In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every 3 days starting from 10 days following implantation to pregnant rabbits at intravenous doses of 2 mg/kg per kg, or every six days during organogenesis at subcutaneous doses of 3 mg per kg. In these studies, aflibercept caused a decrease in fetal weight and increase in malformations (e.g., rib and skull anomalies) compared to controls. The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg.

7.1 Pregnancy
- Aflibercept is not recommended during breastfeeding.

7.2 Lactation
- Aflibercept is not recommended during breastfeeding.

7.3 Nursing Mothers
- Aflibercept is not recommended during breastfeeding.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
- Pregnancy Risk Summary

8.2 Lactation
- Lactation Risk Summary

8.3 Females of Reproductive Potential
- Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 1 month after the last intravitreal injection of EYLEA.

8.4 Pediatric Use
- Pediatric Use

9. USE IN SPECIFIC POPULATIONS
- Use in the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were 50 years of age or older. No significant differences in efficacy or safety were seen with increasing age in these studies.

10. ADVERSE REACTIONS
- Table 1: Most Common Adverse Reactions (≥5%) in Wet AMD Studies

11. CLINICAL STUDIES
- Table 2: Most Common Adverse Reactions (≥5%) in RVO Studies

12. CLINICAL STUDIES
- Table 3: Most Common Adverse Reactions (≥5%) in DME Studies

13. CLINICAL STUDIES
- Table 4: Most Common Adverse Reactions (≥5%) in Diabetic Retinopathy Studies

14. CLINICAL STUDIES
- Table 5: Most Common Adverse Reactions (≥5%) in Diabetic Macular Edema Studies

15. CLINICAL STUDIES
- Table 6: Most Common Adverse Reactions (≥5%) in Diabetic Retinopathy Studies

16. CLINICAL STUDIES
- Table 7: Most Common Adverse Reactions (≥5%) in Diabetic Macular Edema Studies

17. CLINICAL STUDIES
- Table 8: Most Common Adverse Reactions (≥5%) in Diabetic Retinopathy Studies

18. CLINICAL STUDIES
- Table 9: Most Common Adverse Reactions (≥5%) in Diabetic Macular Edema Studies

19. CLINICAL STUDIES
- Table 10: Most Common Adverse Reactions (≥5%) in Diabetic Retinopathy Studies

20. CLINICAL STUDIES
- Table 11: Most Common Adverse Reactions (≥5%) in Diabetic Macular Edema Studies

21. CLINICAL STUDIES
- Table 12: Most Common Adverse Reactions (≥5%) in Diabetic Retinopathy Studies

22. CLINICAL STUDIES
- Table 13: Most Common Adverse Reactions (≥5%) in Diabetic Macular Edema Studies

23. CLINICAL STUDIES
- Table 14: Most Common Adverse Reactions (≥5%) in Diabetic Retinopathy Studies

24. CLINICAL STUDIES
- Table 15: Most Common Adverse Reactions (≥5%) in Diabetic Macular Edema Studies

25. CLINICAL STUDIES
- Table 16: Most Common Adverse Reactions (≥5%) in Diabetic Retinopathy Studies

26. CLINICAL STUDIES
- Table 17: Most Common Adverse Reactions (≥5%) in Diabetic Macular Edema Studies
Database IDs risk factors for iris damage, dropped nucleus

Rare cataract surgery complications focus of collaboration

By Lynda Charters; Reviewed by Mats H. Lundstrom, MD

THE EUROPEAN REGISTRY for Quality Outcomes in Cataract and Refractive Surgery (EUREQUO) is a collaboration established in 2008 between the European Union and the European Society of Cataract and Refractive Surgery. Data on both cataract and refractive surgeries can be entered through interface or manual input into the two registries contained in the EUREQUO, according to Mats H. Lundstrom, MD. Data from almost 3 million surgeries have been entered into the database to date. The recorded data are comprehensive and reflect the entire range of the relevant information about the cataract surgeries from baseline including demographics, preoperative visual acuity, and risk factors through follow-up including the visual and refractive outcomes and any postoperative complications.

The surgical information reflects the type of surgery and the IOL implanted as well as any surgical complications that might have occurred, such as posterior capsular rupture, vitreous loss, dropped nucleus, iris damage, and any others.

Dr. Lundstrom, who is adjunct professor emeritus in ophthalmology, Department of Clinical Sciences, Ophthalmology, Faculty of Medicine, Lund University, Kariskrona, Sweden, focused on the complications of dropped nucleus and iris damage.

IRIS DAMAGE

In the study period that ranged from Jan. 1, 2008 to Dec. 31, 2018, of the 1,715,348 reported procedures, iris damage during phacoemulsification occurred in 4,971 (0.3%) cases. Analysis of the registry data indicated that the rate of iris damage decreased from 0.41% in 2008 to 0.20% in 2018.

Logistic regression analysis of the surgical data showed that the independent variables related to iris damage were male gender, older age, small pupil, white cataract, poor preoperative visual acuity, and glaucoma (p < 0.001 for all comparisons).

The mean postoperative logarithm of the minimum angle of resolution visual acuity in patients with iris damage was slightly worse than in patients without iris damage, i.e., 0.01 ± 0.22 versus 0.06 ± 0.17, a difference that reached significance (p < 0.001), Dr. Lundstrom reported.

The refractive outcome regarding the mean absolute biometric prediction error was also significantly (p < 0.001) different between patients with and without iris damage, 0.58 D versus 0.43 D, respectively. Those with iris damage also had significantly (p < 0.001) more postoperative complications compared with those who did not, 7.2% versus 2.0%.

DROPPED NUCLEUS

When considering this complication during the same time period and in the same number of recorded surgeries, a dropped nucleus occurred in 1,221 cases (0.07%). This complication also decreased over time, from 0.093% in 2008 to 0.016% in 2018, Dr. Lundstrom reported.

The independent variables that were found by logistic regression analysis to be related to a dropped nucleus included a white cataract, previous vitrectomy, poor preoperative visual acuity, small pupil, pseudexfoliation, diabetic retinopathy, and gender.

Visual outcomes linked with dropped nucleus were worse than those associated with iris damage. The mean postoperative visual acuities in patients with a dropped nucleus compared with those without a dropped nucleus were 0.24 ± 0.32 versus 0.05 ± 0.17 (P < 0.01). The respective mean absolute biometric prediction errors were 1.02 D versus 0.45 D (P < 0.01) and the respective rates of postoperative complications were 18.1% versus 2.0% (P < 0.01). The specific postoperative complications were corneal edema, high intraocular pressure, and endophthalmitis, among others, he reported.

The importance of the EUREQUO to provide such valuable data is underscored by the ability to identify risks factors in patients undergoing cataract surgery. Dr. Lundstrom concluded that iris damage and dropped nucleus have decreased over a decade. Several risk factors have been identified.

“Combinations of risk factors increase the risk,” he said. “The visual and refractive outcomes are worse compared with no complication. The poor outcomes are explained partly by the risk factors.”

CONCLUSIONS

This technique achieved stable extended depth of focus and monomicrovision. High patient satisfaction was achieved in overall visual quality and visual performance over the long term. Overall, 100% of patients were corrected to 20/20 for distance and had 12 uncorrected near vision.

The study authors explained that they believe this is an excellent procedure to correct presbyopia and achieve long-term satisfactory results in the pre-cataract patient.

REFERENCE


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

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Dr. Luger has no financial disclosures related to this content.
Repeat-SLT proves to be successful as long-term treatment option

**By Lynda Charters; Reviewed by Prof Gus Gazzard, FRCOphthMA, MBCHIR, MD**

**REPEAT-SELECTIVE LASER TRABECULOPLASTY (SLT)**, a protocol explored in a subset of patients in the SLT Laser in Glaucoma and Ocular Hypertension (LIGHT Trial), successfully lowered the IOP in eyes in which the IOP increased after 1.5 years after the initial SLT application.

The IOP decrease resulting from repeat-SLT lasted longer than the first round of IOP lowering.

The three-year LIGHT Trial evaluated the initial treatments using SLT laser or medications in patients with glaucoma and ocular hypertension; treatments were increased as required, according to Gus Gazzard, FRCOphthMA, MBCHIR, MD, professor of ophthalmology at UCL University College and consultant ophthalmic surgeon, Moorfields Eye Hospital, London.

The study included only treatment-naïve patients with newly diagnosed primary open-angle glaucoma (POAG) or ocular hypertension in one or both eyes. Patients with advanced disease who could not be treated with laser or medication were excluded from the trial.

A total of 718 patients ultimately were randomly selected to either SLT laser or medication at the beginning of the LIGHT Trial.

At the end of the three years, 91% of patients remained in the study.

The initial standardized SLT protocol included 360º of treatment in which 100 laser shots were applied using a Latina SLT contact lens.

The clinical endpoint was that at which treatment increases were allowed.

In selecting the eyes to undergo repeat-SLT, the investigators also considered the degree of IOP lowering at two months; this value at that time point is strongly predictive of the three-year outcome.

The two-month time point was the first time point at which treatment increases were allowed.

The results also showed that the early failures tended to more often have moderate to more severe POAG, and, therefore, the IOP target was more stringent,” he said.

Dr. Gazzard concluded that repeat-SLT successfully reduced IOP in eyes that failed within 1.5 years of the start of the LIGHT Trial.

“The adjusted absolute IOP reduction, controlling for the pre-treatment IOP, seemed to be greater than after the first laser treatment. The IOP lowering in these eyes seemed to last longer after repeat-SLT.”

- Gus Gazzard, FRCOphthMA, MBCHIR, MD
Device controls pain and inflammation adequately in first, second eye surgeries

By Lynda Charters; Reviewed by John A. Hovanesian, MD

The dexamethasone ophthalmic intracanalicular insert, 0.4 mg (Dextenza, Ocular Therapeutix Inc.) seems to be filling an unmet need by reducing the pain and inflammation after cataract surgery in the second eye to a level that is comparable to pain in the first eye that underwent cataract surgery.

Postoperative pain and inflammation generally are greater after a cataract extraction performed in the second eye compared with an initial cataract extraction in the first eye. As a result, the availability of a drug/device that would lessen or eliminate that pain and inflammation would be a boon to this patient population.

According to John Hovanesian, MD, clinical instructor, UCLA Jules Stein Eye Institute, Laguna Hills, CA, the increased pain in the second eye is hypothesized to result from sympathetic irritation during the surgery in the first eye.

“This makes the fellow eye more prone to painful stimuli, or to memory traces of pain from the surgery in the first eye, however small, that may linger for weeks postoperatively,” he said.

The development of inflammation following the second surgery also is affected by the inflammation in the first eye.

“This may be mediated by the chemical mediators monocyte chemotactant protein-1 and possibly transforming growth factor beta 2, the levels of which are elevated in the second eye at the time of surgery compared with the first eye,” Dr. Hovanesian explained.

The dexamethasone insert, which was FDA-approved in 2019, is put into the punctum of the lower lid after an ophthalmic surgery to provide an anti-inflammatory effect and serves as a substitute for the instillation of corticosteroid drops during the postoperative period. In addition to reducing the postoperative treatment burden, the insert also provides sustained and continuous tapered delivery of dexamethasone for up to 30 days after surgery.

In preparation for the insert to be placed, the lower lid is drawn laterally and the punctum is dilated. Importantly, the surface is dried to prevent the insert from becoming wet and swelling almost immediately, Dr. Hovanesian said.

A phase III study with three study arms was conducted to determine the difference in postoperative pain and inflammation following cataract surgery in the first and seconds eyes of patients who received the dexamethasone insert.

The study included 541 patients randomly assigned to the dexamethasone insert and 385 patients randomly assigned to placebo, with both groups followed for more than 30 days. The primary end point was the absence of pain on Day 8 postoperatively and the absence of anterior chamber cells on Day 14 postoperatively. The safety of the insert also was evaluated.

Almost one-third of the eyes underwent cataract surgery in the second eye, 30.3% in the insert group and 33.2% in the placebo group.

A subgroup analysis of those two groups showed that compared with patients who received dexamethasone and placebo during cataract surgery in the first eyes, there were similar levels of absence of pain and inflammation following surgeries in the second eyes. Evaluation of the use of rescue medications showed as expected that these medications were used more often in the patients in the placebo groups undergoing surgeries in the first and second eyes, Dr. Hovanesian reported.

The safety results, based on the results of a pooled analysis of three arms of the phase III studies, were similar between the patients who received the insert and those who received placebo. Common ocular adverse events, such as anterior chamber inflammation, eye inflammation, reduced vision, corneal edema, and cystoid macular edema, occurred in more than 1% of the eyes that received the insert.

A slightly higher increase in IOP was seen on Day 14 postoperatively.

**Primary Efficacy Results by First- or Second-Eye Lens Extraction**

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*Statistically significant; P≤0.05 ITT + last observation carried forward (LOCF) Population

Phase II study sought to determine difference in postoperative pain, inflammation following cataract surgery.

(Chart courtesy of John A. Hovanesian, MD)

**TAKE-HOME**

- The dexamethasone ophthalmic intracanalicular implant, 0.4 mg may eliminate the need for corticosteroid drops after cataract surgery.
Are topical antibiotics needed after cataract surgery? Maybe

Research finds therapy may not be required, easing burden on patients, physicians

By Lynda Charters; Reviewed by Alexander James Silvester, MBCHB, and Anil Pitalia, MBCHB

LET US BE more specific, topical antibiotics after cataract surgery are not necessary, according to Alexander James Silvester, MBCHB, as long as surgeons tick off all the boxes on the safety check list.

To lessen the postoperative burden on patients who underwent cataract surgery by eliminating the topical antibiotic regimen, Dr. Silvester emphasized that the surgery must be uncomplicated and have no dropped nucleus or posterior capsule rupture. And, importantly, instillation of intracameral antibiotics is a must. Surgeons in the UK have a licensed intracameral antibiotic to rely on, Aprokam (Cefuroxime), that is used in all cases.

While the endophthalmitis rate in the UK is only 0.03% after cataract surgery, the fear is that superbugs will surge ahead and dramatically increase that incidence rate.

“Overuse or inappropriate use of antibiotics is the largest cause of antibiotic resistance,” said Dr. Silvester, an ophthalmologist and medical director of the SpaMedica group of eye hospitals, Bolton, UK.

POST-OP ANTIBIOTICS

Studies over the past eight years; a systematic review (Kessel et al. 2015), a retrospective study of 15,000 eyes (Raen et al. 2013), and review of the Swedish National Cataract Registry (Behndig et al. 2011), supported the notion of eliminating antibiotic drops after cataract surgery.

“All found that topical postoperative antibiotics are not important in preventing endophthalmitis after cataract surgery when the patients have received intracameral antibiotics,” Dr. Silvester said.

Published guidelines from the European Society of Cataract and Refractive Surgeons (ESCRS) in 2018 issued a statement that topical antibiotic drops confer no added benefit over intracameral cefuroxime. A power analysis suggested that a sample of 35,000 patients would be necessary to show that topical antibiotics are unnecessary, he said.

“While endophthalmitis following routine cataract surgery was rare, the incidence rate following cataract surgery in September 2018 at SpaMedica without the use of postoperative topical antibiotics, and no cases of endophthalmitis have developed in that newer larger cohort. There also were no changes in the complications or visual outcomes.

Dr. Silvester concluded by strongly suggesting that topical antibiotics are not needed post-routine cataract surgery, with the caveat that intraocular antibiotics are necessary to reduce endophthalmitis risk.”

Regarding the secondary outcomes, he reported that there were no clinical or statistical differences between the two groups. Anterior uveitis was the most frequent complication that occurred by 3.9% and 3.8%, respectively, in the two patient groups. According to Dr. Silvester, topical antibiotics are not necessary following routine cataract surgery.

“A power analysis suggested that a sample of 35,000 patients would be necessary to show that topical antibiotics are unnecessary,” he said.

Since September 2018, 36,661 cataract surgeries have been performed at SpaMedica without the use of postoperative topical antibiotics, and no cases of endophthalmitis have developed in that newer larger cohort. There also were no changes in the complications or visual outcomes.

Dr. Silvester concluded by strongly suggesting that topical antibiotics are not needed post-routine cataract surgery, with the caveat that intraocular antibiotics are necessary to reduce endophthalmitis risk.”

DEXAMETHASONE

(Continued from page 19)

1, which decreased thereafter, in the dexamethasone group that Dr. Hovanesian believes was related to the viscoelastic agent used.

CONCLUSION

Dr. Hovanesian noted that about a third of the trial participants were undergoing a cataract surgery in the second eye in the dexamethasone and placebo groups.

“The results showed that the control of inflammation and pain was similar in both groups,” he said.

“The dexamethasone was safe and well tolerated in both the eyes of patients that underwent surgeries in the first and second eyes.”

Moreover, Dr. Hovanesian noted that the current results were consistent overall with the pooled data in the pivotal study.

“We believe this is important because if the dexamethasone insert were providing an inadequate level of inflammation control, a different result might be evident, that is, greater inflammation and greater persistent pain would have been evident in the second eyes undergoing cataract surgery,” he concluded.

A power analysis suggested that a sample of 35,000 patients would be necessary to show that topical antibiotics are unnecessary, he said.

Since September 2018, 36,661 cataract surgeries have been performed at SpaMedica without the use of postoperative topical antibiotics, and no cases of endophthalmitis have developed in that newer larger cohort. There also were no changes in the complications or visual outcomes.

Dr. Silvester concluded by strongly suggesting that topical antibiotics are not needed post-routine cataract surgery, with the caveat that intraocular antibiotics are necessary to reduce endophthalmitis risk.”

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This article was adapted from Dr. Hovanesian’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Hovanesian reported receiving grant support from Ocular Therapeutix, Inc.
LBS-008 engages the retinol binding complex in the circulation, and is therefore an oral drug that does not need to be injected intravitreally.

“The drug also induces very rapid clearance of its target, making reduction of RBP4 a very convenient serum biomarker of the treatment’s efficacy in humans,” said Dr. Petrukhin, professor of ophthalmic science, Department of Ophthalmology, Columbia University, New York.

The preclinical studies showed that LBS-008 very effectively inhibited bisretinoid synthesis and preserved the photoreceptor cells in two genetic models of Stargardt disease.

Following the establishment of the drug’s safety, the investigators went to study the safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy human subjects in a phase 1 randomized, double-blind, placebo-controlled, single and multiple-ascending dose study.

In the single ascending-dose study, which has been completed, Dr. Petrukhin and colleagues evaluated 25-, 50-, 100-, 200-, and 400-mg doses in eight subjects per cohort; six subjects of each cohort were treated with LBS-008 and two received placebo.

“The drug showed a slow elimination rate and there was a modest dose-dependent increase in the exposure to the drug, i.e., doses greater than 50 mg did not result in substantially higher exposure,” he said.

Another important finding was the “remarkable” pharmacodynamic effect of the drug on the biomarker. One dose of LBS-008 produced a sustained reduction of serum RBP4 for several days, which, he pointed out, is consistent with a slow elimination rate.

The multiple-ascending dose study looked at 5-, 10-, 12-, and 25-mg doses.

Eight subjects per cohort were evaluated; six were treated with the drug and two with placebo.

“The effect on the biomarker was also very good in this study,” Dr. Petrukhin said. “We were able to induce a sustained reduction in plasma RBP4 below the level that may be associated with clinical efficacy, and at the end of dosing the RBP4 reduction was fully reversible.”

In the single ascending-dose study, one mechanism-based adverse event, mild xanthopsia, occurred in the 100-mg cohort and resolved four days after dosing.

One systemic adverse event occurred, namely, headache, that was considered to be related to the treatment. One ocular adverse effect occurred, mild pinguecula, in the 50-mg cohort that was unrelated to treatment.

In the multiple ascending-dose study, no treatment-related systemic adverse effects occurred, and the most common ocular adverse event was impaired dark adaptation test, but it was not correlated with subjective complaints. All cases returned to normal at the last study visit.

“The combination of adverse events in the multiple ascending-dose study indicates the systemic target engagement that we showed with analysis of the serum biomarker was correlated nicely with the pharmacodynamic effect in the retina,” Dr. Petrukhin said.

Dr. Petrukhin added that the phase I study was a success.

“The drug was very well tolerated systemically and the ocular adverse events were mild, transient, and reversible,” he concluded. “We were able to demonstrate the desired effect on the serum biomarker, and the reduction in RBP4 was below the level that may be considered associated with clinical efficacy in AMD studies. The results indicated that the 10-mg once daily oral dose is the one that may be advanced in future clinical trials in Stargardt disease.”

‘The results indicated that the 10-mg once daily oral dose is the one that may be advanced in future clinical trials in Stargardt disease.’

— Konstantin Petrukhin, PhD

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Dr. Petrukhin invented this technology and is a consultant and advisor to Belite Bio, a US biotechnology company.
Module bridges remote gap in learning, mentorships
Platform can link healthcare specialists from around the world for training, consultations

By Lynda Charters; Reviewed by Hunter Cherwek, MD

Orbis International has one of the largest and most diversified ophthalmology resource offerings in the world, and what it offers is completely free, with the goal of using technology to scale up its efforts to eliminate avoidable blindness in developing countries.

Cybersight, founded by Gene Helveston, MD, in the late 1990s, is the free eye health learning and mentorship telemedicine platform used by Orbis International to teach and disseminate information as part of its mission to prevent and treat avoidable blindness. Since the time when Dr. Helveston sought to teach strabismus procedures to Cuban physicians, Cybersight has evolved substantially to incorporate the Cybersight Consult, Cybersight Learn, and Cybersight Live Teaching components into its program.

“All of these areas are about building capacity in human resources in the low- to middle-income countries in which we work,” said Hunter Cherwek, MD, who is vice president, clinical services, Orbis International.

According to Dr. Cherwek, in the area of consultation, more than 150 top international ophthalmology experts are serving as mentors, and there have been more than 20,000 patient consultations undertaken for complex cases to date.

“We have been involved in 950 cases of retinoblastoma and linked doctors worldwide to St. Jude’s Hospital in Memphis and Toronto Sick Children’s Hospital in Canada,” he said. Dr. Cherwek noted Cybersight Learn offers online courses and an open-access library in topics related to ophthalmology, nursing, and associated fields.

“Doctors can go online free of charge and take multi-hour courses in, for example, phacoemulsification, small incision cataract surgery, pediatrics, and glaucoma,” he said.

Cybersight Live Teaching offers live lectures and surgical demonstrations through real-time video conferencing, Dr. Cherwek explained, adding that it has been an explosive field for the company’s platform.

“We are using artificial intelligence to enable our consultants not only to teach our doctors what the diagnosis is but also how the diagnosis was derived, what algorithmic thinking was used, and how the ocular structures and associated factors are viewed,” he said.

The courses offered are not just for ophthalmologists but also include nurses, optometrists, schoolteachers, and community village workers. The online courses that are proving to be of special interest are those providing instruction in phacoemulsification and small incision cataract surgery, the latter of which is the most highly accessed course.

Cybersight is a health learning and mentorship telemedicine platform that physicians can access from anywhere. (Photo courtesy of Hunter Cherwek, MD)

The data collected from 2018 boast about the increasing numbers of surgeons taking advantage of the resources offered by Cybersight:

- 5,052 new users bring the total number of users to more than 12,000 globally;
- 2,160 patient consultations; and
- 89 live webinars in 2,868 locations in 127 countries. The webinars and online courses trained 5,872 people in 165 countries.

The courses offered are not just for ophthalmologists but also include nurses, optometrists, schoolteachers, and community village workers. The online courses that are proving to be of special interest are those providing instruction in phacoemulsification and small incision cataract surgery, the latter of which is the most highly accessed course.

MOBILE ACCESS
For Dr. Cherwek, the most exciting technologic advances are smartphone apps being used, for example, to enable tribes to move their cattle from place to place in anticipation of changing weather patterns. The mobile utilization of Cybersight has increased markedly from 2017 to 2019, compared with desktop access, he reported.

“It is exciting to see how much we have been able to democratize education and open up access via cell phone technology,” he emphasized.

REMOTE WET LABS
Dr. Cherwek described the creation of academic bridges through the Cybersight platform with wet labs that have been established worldwide.

“We have normalized remote surgical mentorship in Peru and have the equipment ready to expand to Ghana, Cameroon, South Africa, Indonesia, and Bolivia,” he said.

In this teaching model, international ophthalmology experts observe and mentor local surgeons in real time during live surgery, from thousands of miles away.

The digital wet lab model, he explained, is now in Peru and at Emory University, and new equipment is on-site at Shroff’s Charity Eye Hospital in India. The wet lab courses now have standardized curricula, and individuals must be able to demonstrate knowledge and basic science competency before entering the wet lab in Peru. Based on this experience, the residents receive grades based on the Ophthalmology Surgical Competency Assessment Rubric (OSCAR) score and comments about their surgical performance and then review their surgical videos.

Dr. Cherwek reported the results of a study in which 12 final-year residents who submitted 120 surgical videos were followed. The trainees’ average competency scores increased from 15.9 before training to 25.1 afterward.

Continues on page 23.
Heads-up technology brings ergonomics to cataract surgery

3-D visualization system allows surgeons to operate more efficiently, effectively

By Cheryl Guttman Krader; Reviewed by Robert J. Weinstock, MD

THE SAFETY AND efficiency of cataract surgery performed using a heads-up 3-D visualization system (NGenuity 3D Visualization System, Alcon) seems similar to a traditional approach using a binocular microscope, according to Robert J. Weinstock, MD.

His conclusion was based on the findings of a retrospective study including 2,180 routine cases that found no statistically significant differences between the two techniques in operating time or rate of posterior capsular rupture and vitreous prolapse.

“By eliminating the need to look through the oculars of the microscope, this technology allows for better posture,” he said. “Therefore, its implementation of the heads-up technology may overcome work-related disability and help surgeons perform better with less pain and fewer neck and back problems.”

Dr. Weinstock noted that it is possible that over time, studies may show that a more comfortable operating environment for the surgeon may translate into better outcomes for patients. With the heads-up system, the surgeon wears goggles and visualizes the surgical field on a 3-D OLED monitor.

STUDY FINDINGS

For the retrospective study, Dr. Weinstock analyzed data from a consecutive series of cases he performed between August 2016 and July 2017. (During the study period, the heads-up system was available as TrueVision 3D Visualization, TrueVision Systems. It was subsequently acquired by Alcon and rebranded as NGENUITY.)

Dr. Weinstock said he excluded patients with any preoperative clinical findings that would be expected to result in a complication or longer duration of surgery (e.g., history of trauma, iris synchiae, small pupil, pseudoxfoliation syndrome, phacodonesis, hypermature cataract). Patients receiving a toric IOL were excluded because of time needed for IOL positioning.

The heads-up visualization group included 1,573 eyes, and there were 617 eyes that had traditional cataract surgery. Posterior capsular tear/vitreous prolapse occurred in 12 cases in the traditional group (0.76%) and five cases in the heads-up group (0.31%), respectively. The heads-up group had 11 cases of vitreous prolapse and four cases of retinal detachment.

Operating time was 6.52 ± 1.38 min for the group that had traditional surgery. Posterior capsular tear/vitreous prolapse occurred in 12 cases in the heads-up group and five cases in the traditional group (0.76% and 0.81%, respectively).

IMPROVING TECHNOLOGY

Dr. Weinstock noted that it is possible that over time, studies may show that a more comfortable operating environment for the surgeon may translate into better outcomes for patients. With the heads-up system, the surgeon wears goggles and visualizes the surgical field on a 3-D OLED monitor.

TAKE-HOME

◗› Study comparing groups of cataract patients operated on using a 3-D visualization system or with the surgeon looking through oculars found no between-group differences in mean operating time and rate of intraoperative complications.

With the Cybersight Consult function, the primary purpose is to link clinic personnel in these countries to ophthalmology experts worldwide.

“We can now do this using digital photography and the Internet to link any two eye health professionals,” he said.

In Cybersight Learn, all of the content is free and is being translated almost instantaneously into more than 35 languages.

“This has become a learning management system not just of basic science but for evaluating residents’ wet lab training, OSCAR scores, and videos,” he noted.

The Cybersight Live Teaching component provides live global webinars on clinical and surgical topics. Dr. Cherwek acknowledged the work of Dan Neely, MD, a pediatric ophthalmologist who devotes 20% of his time to Cybersight, and is linked with all of the pediatric ophthalmologists he has trained in Mongolia, Peru, and elsewhere. From Indiana University, he has participated in surgeries in real time and provided surgical coaching.

RESOURCE

(Continued from page 22)

Among 60 resident surgeries performed after training, the patients’ vision exceeded 20/60 in 91.7% of cases, compared with 76% at baseline.

CYBERSIGHT INSIGHT

Cybersight is, first of all, a product that is free to people in low- to middle-income countries. However, it is ultimately a platform, according to Dr. Cherwek.

With the Cybersight Consult function, the primary purpose is to link clinic personnel in these countries to ophthalmology experts worldwide.

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Dr. Cherwek has no financial interest in any aspect of this report.
AI-enabled tool offers glimpse of glaucoma-related functional loss

Technology provides objective, multi-layered information for physicians

By Cheryl Gutman Krader; Reviewed by Siamak Yousefi, PhD

AN ARTIFICIAL INTELLIGENCE-enabled radar holds promise for providing better visual functional assessment of patients with glaucoma compared to currently available tools, according to Siamak Yousefi, PhD.

The glaucoma radar is being developed for use in clinical practice and glaucoma research as a personalized staging and monitoring tool for glaucoma assessment. It provides three layers of knowledge about the disease—severity of global visual functional loss, extent of visual functional loss in hemifields, and local patterns of visual functional loss. It can identify rapid and slow progressing eyes and retain data from thousands of past glaucoma patients.

According to Dr. Yousefi, assistant professor, Department of Ophthalmology and Department of Genetics, Genomics, and Informatics, University of Tennessee, Memphis, TN, visual function assessment of patients with glaucoma is typically done using standard automated perimetry.

“This technique is well established, most of the methods for longitudinal visual field data analysis have a number of limitations,” he said. “The algorithms rely on traditional paradigms such as linear progression, but glaucoma progression may be nonlinear, especially at the later stages of disease. In addition, they generate a binary outcome of progression or no progression, adopt ad-hoc rules to identify progression, and lack advanced visualization and interpretation.”

Dr. Yousefi explained that the artificial intelligence radar is an advanced computational tool that can provide more detailed analyses.

“It can generate an informative, objective outcome with multiple layers of glaucoma knowledge that may enable development of more interpretable models,” he said.

DEVELOPMENT

The radar was developed using more than 13,000 visual fields from more than 8,000 subjects. Principal component analysis was applied to linearly reduce the number of dimensions and extract the global characteristics of the visual fields, and manifold learning was applied to identify the local patterns of visual field loss...

The map or “cloud” of datapoints from the 13,000+ visual fields was then annotated by first identifying very dense regions of the visual field and then applying unsupervised clustering which identified 32 nonoverlapping clusters representing visual fields at different levels of severity.

The 32 clusters on the radar “dashboard” had different mean deviation of the visual fields corresponding to pattern of global visual functional severity with normal eyes located on the right side of the dashboard and eyes with severe visual functional loss at the left and bottom left corner.

Superior and inferior hemifield severities were also computed and mapped, and it was noted that the artificial intelligence pipeline put eyes with similar hemifield characteristics into different clusters even though their global severity may be statistically similar. The researchers also developed a method to identify and decompose visual fields of eyes in each cluster into 17 different patterns of visual field loss and showed that the tool could identify local patterns of visual functional loss.

Validation of the radar was achieved using visual fields from two independent benchmark datasets. The testing demonstrated that cases of confirmed progression consistently followed the direction of visual functional worsening on the dashboard whereas eyes with stable function showed no worsening. The tool performed with 94% specificity and 77% sensitivity.

Individual cases involving patients with serial visual fields acquired over a period of approximately 10 years also illustrated the performance of the tool for showing that the glaucomatous-related functional loss was progressing or remaining stable.

“Using the radar to monitor patients with glaucoma can help guide treatment decisions,” Dr. Yousefi said. “Based on their experience with the radar, clinicians might forecast the next step in a patient’s glaucoma progression and taking into account factors such as its impact on visual function and quality of life, thus adjust the treatment plan.”

Going forward, Dr. Yousefi and colleagues will be validating the model using more clinical data and looking into how to integrate the tool into the clinic.

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This article was adapted from Dr. Yousefi’s presentation at the 2019 meeting of the American Academy of Ophthalmology. The project has funding support from the National Eye Institute. Dr. Yousefi has no other relevant financial interests to disclose.
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GX-314 (REGENXBIO) gene therapy, delivered subretinally to patients with neovascular age-related macular degeneration (AMD), who required a large number of prior injections of anti-vascular endothelial growth factor (VEGF) annually, provided a marked decrease in the number of injections needed and retained or improved the vision and anatomy in this challenging patient population.

RGX-314 uses a proprietary gene delivery platform that is hypothesized to deliver longer and higher protein expression with a lower immune response that earlier generation adeno associated viruses (AAVs) used for gene therapy.

“The AAV8 vector is encoded to deliver a gene that leads to anti-VEGF antibody fragment protein production within the retina,” said Jeffrey S. Heier, MD, co-president and director of Retinal Research, Ophthalmic Consultants of Boston.

All 42 patients included in this study had undergone previous treatment for neovascular AMD and had a “high need” for anti-VEGF therapy, i.e., patients received more than 30 injections on average prior to coming in and an average of 9.6 annualized injections in the year prior to RGX-314. In addition, the included patients had to have shown an anatomic response to anti-VEGF therapy during screening. After RGX-314 was delivered to the subretinal space, the patients were evaluated monthly to assess safety and the need for additional anti-VEGF therapy. Dr. Heier noted.

Re-treatment with an anti-VEGF drug could be provided beginning at four weeks after RGX-314 was delivered and then as needed every four weeks thereafter based on physician discretion, Dr. Heier explained. The criteria for retreatment was per investigator discretion which included choroidal neovascularization-related increased, new, or
Following delivery of RGX-314, Dr. Heier reported that the drug was well tolerated. No serious adverse events were reported; most adverse events were classified as mild, i.e., grade 1 in 79% of cases. In addition, no clinically determined immune responses occurred.

Two deaths that occurred were not related to RGX-314. Two serious adverse effects that were related to the delivery procedure were reported, specifically, a peripheral retinal detachment that was repaired successfully and a case of endophthalmitis that occurred after collection of an aqueous sample.

“We observed a dose-dependent increase in RGX-314 protein across the five dose cohorts,” he reported. The protein levels were measured in aqueous samples collected one month after delivery of RGX-314.

Cohort 3, which included six eyes treated with a dose of $6 \times 10^{10}$ genome copies (GC)/eye, demonstrated the highest clinical response seen in the trial with stable to improved vision and anatomic outcomes. Nine of the 12 patients were injection-free at five to six months.

Cohort 4, which included 12 patients treated with a dose of $2.5 \times 10^{11}$ GC/eye, demonstrated an interesting analysis of the incomplete responses as the result of fluid, or a new ocular hemorrhage.

Five of the 12 patients were injection-free at 6 months. The average improvement at that time point was $+2$ letters and the decrease in the central retinal thickness was $-42 \, \mu m$.

Two patients in this cohort continued to require anti-VEGF monthly injections as the result of incomplete responses to anti-VEGF therapy.

Cohort 5, which included 12 patients treated with a dose of $2.5 \times 10^{11}$ GC/eye, demonstrated the highest clinical response seen in the trial with stable to improved vision and anatomic outcomes.

Nine of the 12 patients were injection-free at five to six months with vision of $+5$ letters and a decrease in central retinal thickness of $-80 \, \mu m$ over five months.

“Cohort 5 demonstrated the highest clinical response observed,” Dr. Heier commented.

An interesting analysis of the injections administered to patients in cohort 5 in the year before they were treated with RGX-314 showed injections ranged from six to 13. After delivery of RGX-314, only three patients needed additional therapy, i.e., six injections for one patient with an incomplete anti-VEGF response, two injections for a second patient, and one injection to a third patient.

In the case of the cohort 5 patient who required 13 injections with persistent subretinal fluid at every visit in the year prior, Dr. Heier reported that following delivery of RGX-314, this patient remained dry and did not need rescue injections for five months.

Dr. Heier noted that based on the study findings, Regenxbio plans to move forward with phase Ib study of RGX-314 for wet AMD and an Investigational New Drug trial for diabetic retinopathy. The company also will be investigating suprachoroidal delivery using the ClearSide Microinjector, which can be used in-office.

“Subretinal RGX-314 was well tolerated in the five study cohorts. A dose-dependent increase in ocular protein was observed across the cohorts.”

Jeffrey S. Heier, MD

THE RESULTS

Dr. Heier noted that based on the study findings, Regenxbio plans to move forward with phase Ib study of RGX-314 for wet AMD and an Investigational New Drug trial for diabetic retinopathy. The company also will be investigating suprachoroidal delivery using the ClearSide Microinjector, which can be used in-office.

“Subretinal RGX-314 was well tolerated in the five study cohorts. A dose-dependent increase in ocular protein was observed across the cohorts.”

Jeffrey S. Heier, MD

TAKE-HOME

➢ RGX-314 gene therapy, a treatment for wet age-related macular degeneration delivered subretinally, showed dose-dependent sustained/improved vision and a good safety profile.
Examining the long and winding road of gene therapy research

Overcoming challenges, physicians, researchers turn genetic science into medicine

By Cheryl Guttman Krader

There is no question that retinal gene therapy has arrived. Not only is it alive and well today, but looking at the current state of research, it will hopefully have a very bright future.

These were some of the messages contained in the 2019 Charles L. Schepens MD Lecture Award given by Jean Bennett, MD, PhD, and Albert M. Maguire, MD, at the American Academy of Ophthalmology 2019 annual meeting in San Francisco.

They shared their experiences developing voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), the first gene therapy approved in the United States to treat an inherited disease.

“When we began this research, there was no such thing as gene therapy,” said Dr. Maguire, professor of Ophthalmology, University of Pennsylvania. “There were no clinical trials, no companies, no laboratory techniques to do retinal gene transfer. Our original Leber’s congenital amaurosis (LCA) team numbered just six people.”

Dr. Maguire pointed out that gene therapy “is a multibillion dollar business involving countless investigators, dozens of startups, and several large pharmaceutical companies, all employing thousands of people.”

Dr. Bennett provided a clinical status update.

“There are now more than 1,150 patients enrolled in retina gene therapy clinical trials that are being conducted at more than 30 sites, and at least 13 Centers of Excellence are administering Luxturna,” she said. “Importantly, there are many more gene therapy clinical trials being planned, and we hope that Luxturna is just the first of many successful gene therapies.”

How it all began

Dr. Bennett, professor of Ophthalmology; Cell and Developmental Biology, University of Pennsylvania, recounted that Dr. Maguire first asked her in 1985, when they were both still in medical school, if she thought it would be possible to transfer genes to the retina.

Although Dr. Bennett said yes, she recognized the path forward would be difficult because there were no foundations to build on.

“There were no genes to work with, no animal models, no delivery vectors, no surgical methods, no outcome measures, and no funding,” she said.

After developing an effective vector for gene delivery to the retina, the proof of concept study was carried out in a canine model of RPE65 LCA. Treatment benefit was demonstrated through assessments of electroretinography, nystagmus, pupillary light reflex, and ability to function outdoors as well as in a mobility test, which led to early interest in developing a mobility test for patients.

Dr. Bennett credited the success of the preclinical development program to a number of steps that were taken early on to ensure the efficiency of gene delivery and success of the surgical procedure, and she described those measures.

Turning science into medicine

Dr. Maguire described the many challenges and surprises encountered as the research moved toward and through the clinical development pathway. First, the researchers faced a negative environment.

“Gene therapy was a novel concept that was widely viewed with skepticism and suspicion,” Dr. Maguire said. “The death of Jesse Gelsinger (the first person who died in a clinical trial for gene therapy) had cast a pall over the field, and the fallout was paralyzing.”

It was necessary to become educated about the complex regulatory requirements of drug development and navigate the problematic ethics of performing a clinical trial in the vulnerable pediatric population.

After positive results were achieved in the phase I study, problems were encountered in planning the phase II trial. The researchers were faced with the need to design and validate a new primary endpoint that the FDA would accept as clinically meaningful—thus the creation of the multimobility test.

Choosing the control group for the phase III trial was also not straightforward.

The early success achieved with the retinal gene therapy was generating high patient interest among potential candidates, but everyone wanted to be in the treatment arm, Dr. Maguire explained.

“FDA regulations, however, stipulated the need for an untreated control population. A design in which the control group received delayed treatment after one year was acceptable to patients and satisfied the FDA,” he said.

Dr. Maguire concluded by describing a final surprise, noting that the enthusiasm of the advisory board that reviewed voretigene was another thing that was not anticipated.

“Our application asked for approval to treat children 3 years and older, but the FDA Advisory Committee recommended approval for children as young as 1 year of age, and that is where it stands today,” said Dr. Maguire. “It is a peculiar position to be told to do more, not less surgery.”

In December, 2017, voretigene was approved by the FDA for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. In November 2018, it received marketing authorization from the European Commission.

Take-home

» Retinal gene therapy is making a move from science fiction to science fact. With research advancing the technology almost daily, it will have a bright future in the field of ophthalmology.

When we began this research, there was no such thing as gene therapy. There were no clinical trials, no companies, no laboratory techniques to do retinal transfer."

- Albert M. Maguire, MD

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Dr. Maguire has no financial interests to disclose.
Structure-function discordance common in glaucoma

Understanding mechanisms of disease provides guidance for clinical decisions

By Cheryl Guttman Krader; Reviewed by David S. Greenfield, MD

Structural and functional measurements are both necessary to monitor for glaucoma progression, but their findings often do not coincide.

David S. Greenfield, MD, has reviewed data on the frequency of test discordance, contributing factors, and strategies to help reconcile the differences and improve agreement.

A common phenomenon

Dr. Greenfield, professor of ophthalmology, Douglas R. Anderson Chair in Ophthalmology, Co-Director Glaucoma Service Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, said mechanisms for discordance emphasized that structural and functional assessments in glaucoma often disagree.

Supporting his comment were data from a recently published study conducted at Bascom Palmer Eye Institute, [Nguyen AT, et al. Ophthalmol Glaucoma. 2019;2:36-46]. The study analyzed data from 147 eyes that were followed annually for a mean of almost six years with visual field testing and OCT measurements of the retinal nerve fiber layer (RNFL) and macula. It found that progression was documented by all three metrics in only 7% of eyes.

“The relationship between standard automated perimetry mean deviation (MD) and retinal ganglion cell (RGC) counts is very much dependent on the stage of disease,” said Dr. Greenfield.

He explained, “In eyes with early glaucomatous damage, changes in RGC counts correspond to small changes in MD but much larger changes in RNFL thickness measurements over time. Conversely, in eyes with advanced glaucoma, changes in RGC counts correspond to larger changes in MD but only small or no changes in average RNFL thickness.”

Poor test sensitivity is another factor that can account for discordance between structural and functional tests. In particular, eyes with severe glaucoma can reach a measurement floor below which further changes are no longer detectable.

Differences in the methods for analyzing change represent another issue. Regions of retinal topography may not directly correspond with the same regions of the visual field, and testing strategies may differ based upon linear or logarithmic scaling.

Measurement variability and poor quality data can also lead to discordance. Poor image quality is common and may be seen in 25% to 30% of scans and often result from eye movement, shadowing associated with ptosis or eyelid blink, or algorithm failure.

Cases with discordance

The first thing that clinicians should do when structural and functional results disagree is to repeat testing in eyes with poor quality imaging or unreliable visual fields.

Incorporating ancillary diagnostic testing, such as central 10° visual fields and macular ganglion cell measurements, are also very useful adjuncts to reconcile structure-function discordance.

Clinicians should recognize that challenges with imaging exist in eyes with severe glaucoma, given the increased measurement variability, reduced signal-to-noise ratio, potential for algorithm failure, and measurement floor which may limit progression detection, Dr. Greenfield said.

Dr. Greenfield also recommended using change detection algorithms which incorporate statistical models to measure glaucoma progression.

“Avoid using summary parameters, such as average thickness values, because they tend to be insensitive to localized change,” he said. “It is very important to carefully assess the rates of progression in order to determine the velocity of change.”

When assessing discordance between SAP and OCT measures, clinicians should carefully examine the optic nerve for disc hemorrhage because clinical trial evidence supports its role as a biomarker for progression.
ANTERIOR SEGMENT OPTICAL coherence tomography (AS-OCT) has utility for a number of different applications.

David Huang, MD, PhD, described features of the available systems and reviewed some uses for AS-OCT. Dr. Huang is Peterson Professor of Ophthalmology and professor of Biomedical Engineering, Oregon Health and Science University, Portland, OR.

Clinicians can now choose from a number of commercially available AS-OCT systems. The units include devices developed for retinal imaging that have been additionally adapted for corneal imaging and instruments that are dedicated for anterior segment imaging.

‘With their greater depth, the dedicated systems can image the entire anterior segment from the cornea to the lens. Unfortunately, the dedicated AS-OCT systems are only marketed outside the United States at the current time.’

- David Huang, MD, PhD

The two types of devices differ in wavelength. The combination retinal/corneal imaging devices are all 840 nm wavelength spectral-domain systems and have a benefit of higher axial resolution (3 to 9 μm). In contrast, the dedicated AS-OCT devices are 1,310 nm swept-source systems that give better penetration but at the cost of lower resolution of approximately 10 μm.

“With the 840 nm systems, it is possible to delineate the corneal epithelium and endothelium, Bowman’s layer, and the LASIK flap interface,” Dr. Huang said. “It is more difficult to see these thin structures at the 1,310 nm wavelength, but the reduced scattering loss at the longer wavelength allows more consistent visualization of deeper structures such as the scleral spur, angle recess, and even the ciliary body.”

The dedicated AS-OCT platforms also scan deeper (10-11 mm versus 2-6 mm).

“With their greater depth, the dedicated systems can image the entire anterior segment from the cornea to the lens,” Dr. Huang explained. “Unfortunately, the dedicated AS-OCT systems are only marketed outside the United States at the current time.”

APPLICATIONS

All of the AS-OCT instruments can be used to precisely map corneal pachymetry and epithelial thickness. The current state of the art for systems commercially available in the United States is to provide a 9 mm scan width with automatic segmentation and diagnostic parameters that are used to screen for keratoconus and distinguish between various types of corneal shape irregularities.

In keratoconus (including forme fruste keratoconus), the epithelial thickness map will show focal thinning at the apex of the cone where the topography map shows anterior steepening, in sharp contrast to the base of the cone where the epithelium is thicker and the topography is flatter. This inverse relationship between the epithelial thickness and anterior topographic curvature is also found in post-LASIK eyes—the central epithelium is thicker after myopic LASIK and thinner after hyperopic LASIK.

Dr. Huang categorizes the epithelial changes in both keratoconus and post-LASIK corneas as “secondary epithelial modulation.” This contrasts with the other category he terms “primary epithelial deformation” where focal epithelial thickening is the cause of topographic steepening at the same location. This latter group includes contact lenses-related corneal warpage, epithelial basement membrane dystrophy, and dry eye. In these conditions, the topography shows steepening with epithelial thickening.

AS-OCT can also be used to measure topography, and the corneal power value that is provided can be used for IOL power calculation. Dr. Huang’s research group, the Center for Ophthalmic Optics and Lasers, have developed an OCT-based IOL formula for post-LASIK cataract surgery that works with Optovue’s AS-OCT systems. It is posted on the lab website (www.COOLLab.net) and is also accessible as one of the formulas used in the ASCRS IOL calculator (www.iolcalc.org).

“The corneal power value that is generated by AS-OCT represents total corneal power from measurement of both the anterior and posterior corneal surfaces. Our research shows that in post-myopic LASIK eyes, the AS-OCT based IOL power calculation performed better than other formulas recommended for post-LASIK eyes, and other investigators have found that it performed as well as other methods such as the Haigis-L formula and intraoperative aberrometry,” Dr. Huang said.

CONCLUSION

“These findings suggest that the AS-OCT based IOL power calculation may be a good addition to other formulas when performing cataract surgery in these challenging cases.”

Most recently, the capability of AS-OCT has been expanded to non-invasive angiography. Dr. Huang and coworkers have used AS-OCT angiography to image blood vessels in the cornea and the iris. So far, their research has showed that the depth of neovascularization in the cornea varied depending on the cause of the pathologic vessels. It also identified differences in the features of iris vessels associated with benign and malignant tumors.
MILD TRAUMATIC BRAIN injury (TBI) in pediatric patients can result in a variety of visual function deficits, according to Mitchell B. Strominger, MD. Dr. Strominger, a pediatric ophthalmologist and neuro-ophthalmologist at Renown Medical Center, Reno, NV, and professor of Surgery, Ophthalmology, and Pediatrics, University of Nevada Reno School of Medicine, focused on abnormalities involving control of eye movement that can be seen after mild TBI and discussed new information from studies using functional magnetic resonance imaging (fMRI) to investigate the neurocognitive consequences of these events.

Impairment of saccadic eye movements is one type of visual dysfunction that can occur after mild TBI. Another is self-paced saccades. “With bedside evaluation of saccadic eye movements, most patients with mild TBI test will test normal, needing just one saccade to acquire the target,” Dr. Strominger said.

Smooth pursuit eye movements can also be affected after mild TBI. In testing of smooth pursuit, patients with TBI have been shown to have decreased target position, increased eye position error, and variability of eye position.

Vergence eye movements can also be affected after mild TBI. Convergence insufficiency is common. Signs and symptoms include impaired near point of convergence, double vision, and loss of place while reading. It may also be accompanied by accommodative insufficiency with a decrease in accommodative amplitude.

Testing for vergence dysfunction should be done using an accommodative target. Vestibulo-ocular reflex dysfunction also occurs in mild TBI. Affected patients complain about vertigo and oscillopsia. Spontaneous nystagmus is possible, although Dr. Strominger said he has only seen that in a single case.

“The child was evaluated 15 minutes after suffering a concussion,” he noted. “Most patients are not seen for days after the injury.”

EMERGING CONCERNS

MRI scans will be normal in patients with mild TBI, but investigations using fMRI are generating concerning findings about the functional consequences of mild TBI in the pediatric population, Dr. Strominger said.

One study evaluated college athletes 10 to 15 days after a concussive event. Although neurocognitive assessments across six domains showed no evidence of impairment, fMRI demonstrated that compared with normal subjects, the concussed athletes demonstrated increased connections between areas of the brain that underlie executive function.

The findings were different in a study that included younger patients (mean age 14 ± 2 years) who had sustained mild TBI. The athletes in this study showed reduced working memory accuracy than controls that was associated with reduced activity in the dorso-lateral prefrontal cortex, which is the area of the brain underlying executive function.

“The findings in this study suggest that these younger individuals may be unable to engage compensatory strategies to maintain cognitive performance following mild TBI and might explain why some youths appear to have long term problems with cognitive function following a concussion,” Dr. Strominger concluded. “Importantly, the study also indicates that the immature brain is not more plastic to diffuse injury as has been believed but instead is more vulnerable.”

TAKE-HOME

Eye movement dysfunction is one consequence of mild traumatic brain injury in pediatric patients. Emerging data from studies using functional magnetic resonance imaging show new information about neurocognitive impairment.
A novel method of noninvasively evaluating the outcomes after crosslinking is under development. The software that can be plugged into existing topographers will become commercially available in the near future.

“A decade after crosslinking was developed, the question remains about what actually determines the true outcomes of crosslinking; is it flattening or the demarcation line? We have numerous topographers available, but what are we missing?” asked Gairik Kundu, MBBS, MS, a fellow, Department of Cornea and Refractive Surgery, Narayana Nethralaya, Bangalore, Karnataka, India.

An important consideration regarding topographers is how perfect the technology is and what are their limitations. Some devices are based on Scheimpflug and others on Placido. Placido devices can image the anterior but not the posterior corneal surface; however, the technology it is affected by changes in corneal irregularities and alterations of the ocular surface. The Scheimpflug camera does not have sufficient resolution to delink the epithelium from the surface of Bowman’s layer, according to Dr. Kundu.

“It is important for us to understand that the current topographers cannot dissociate the epithelium,” he said.

Another extremely important factor to consider after crosslinking is that the epithelium might be a “masquerader,” Dr. Kundu suggested.

“Is the epithelium the confounder? Is this the factor that we are not actually looking at?” he asked.

The epithelium, he pointed out, can change after crosslinking. The curvature at the air/epithelium interface will differ from that at the epithelium/Bowman’s interface.

“Knowing this, are we seeing the actual outcomes?” Dr. Kundu asked.

Not all outcomes after crosslinking are necessarily the desired ones. This can happen as the result of progression. This is the point at which surgeons must question what is being measured and what should be measured.

“Are we looking at the air/epithelium interface?” Dr. Kundu asked. “In most cases, this is the masquerader that actually masks the changes that are taking place beneath.”

The investigators questioned if this could help them in evaluating crosslinking outcomes postoperatively. Dr. Kundu explained that when they determined the degree of flattening from preoperatively to postoperatively of the anterior surface followed by the stromal surface, they found that the Bowman’s surface had 55% more flattening compared to the air/epithelium interface. He recounted a case in which the anterior surface topography after crosslinking flattened by about 1.05 D.

“When we applied our algorithm and used the virtual de-epithelialization technique the flattening was found to be actually more than 2 D six months postoperatively,” he said.

In a second case, the anterior surface flattening was about 3.5 D after crosslinking, but Bowman’s surface had flattened by almost 1 D.

Dr. Kundu pointed out two known factors: the curvature is known to be steeper on the stromal surface compared with the anterior surface, and that the stromal changes are masked by the epithelial thickness and haze that hide that crosslinking outcomes.

The current study added four important points, according to Dr. Kundu.

“This method provides a non-invasive way to quantify tomographic features at the Bowman’s surface and early detection of diseases and progression,” he concluded. “Bowman’s surface actually shows the real crosslinking outcomes. This method facilitates customized treatments and prevention of unnecessary retreatments in patients with keratoconus.”
Diagnostic advances offer glimpse of endophthalmitis pathogens

By Lynda Charters; Reviewed by Russell Van Gelder, MD, PhD

**ENDOPHTHALMITIS IS ONE** of the most feared consequences of surgery in the United States—the pathology is a purulent inflammation of the aqueous and vitreous that is usually the result of infection.

In addition to its appearance post-operatively, it also may be endogenous or sterile, according to Russell Van Gelder, MD, PhD.

The incidence rates of endophthalmitis following cataract extraction vary from 0.03% to 0.1% in large studies, and the incidence rates following injections vary from 0.05% to 0.1% in large studies.

“Because of the increasing number of injections administered to treat macular degeneration, the incidence of endophthalmitis has re-emerged as a significant public health issue,” said Dr. Van Gelder, holder of the Boyd K. Bucey Memorial Chair and professor of ophthalmology, University of Washington School of Medicine, Seattle.

Though most cases prove to be coagulase-negative *Staphylococcus*, Dr. Van Gelder noted that a wide variety of pathogens have been associated with the infection, including gram-negative, fungi, and other organisms. Interestingly, the Endophthalmitis Vitrectomy Study reported a 30% rate of culture negativity, and other studies have suggested up to 50% culture-negative rate.

**IDENTIFYING THE PATHOGENS**

Microbial disease diagnosis was revolutionized with the introduction of polymerase chain reaction technology (PCR).

“This is a technology that can amplify minute amounts of DNA to facilitate analysis. When applied to microbes, the presence of microbial DNA is considered to be evidence of potential infections,” Dr. Van Gelder explained.

Primers can amplify all bacteria and demonstrate the bacterial DNA in a sample via 16S metagenomics, a method that relies on the fact that all bacteria have a conserved structure to their 16S ribosomal DNA that is amplifiable.

“The conserved sequences form the basis of the primers, and the intervening sequences are unique to the bacteria. By sequencing, the bacteria can be identified definitively by the intervening sequences,” he said.

Biome representational in silico karyotyping (BRiSK) is a technology developed by Dr. Van Gelder and Aaron Lee, MD, to identify pathogens.

“Using this method, about 1% of the DNA in a sample is sequenced exhaustively to identify each existing bacteria,” he explained.

Whole genomic shotgun sequencing has become a more feasible method of identifying pathogens because of reductions in the costs of sequencing.

“In this procedure, all the DNA in a sample is fractionated for human bacteria, all is sequenced, and sequence is parsed piece by piece to determine the bacterial, fungal, viral, or human components,” Dr. Van Gelder explained.

Regarding the efficacy of 16S metagenomics compared with conventional methods of diagnosing endophthalmitis, a recent Indian study (Br J Ophthalmol. 2019;103:152-156) found that the technology was about 100% correct in identifying the organisms determined by culture; in culture-negative cases, PCR showed that about half of those cases were positive most often for coagulase-negative *Staphylococcus*.

However, nothing is perfect. A drawback of PCR is that the technology cannot tell live from dead bacteria or commensals from pathogenic bacteria, which sets the stage for false-positive results.

Dr. Van Gelder recounted a study in which he and his colleagues evaluated 21 cases (11 culture-positive and 10 culture negative) of endophthalmitis post-operatively using 16S metagenomics and BRiSK. He reported that a comparison of the results of the two procedures showed that most of the culture-positive cases were replicated by the molecular techniques, and 16S PCR identified the same organism or a more specific organism than results of culturing.

“Remarkably, most of the culture-negative cases remained negative by 16S PCR and BRiSK, which suggested a very low bacterial load,” he said.

The investigators went on to quantitative 16S PCR, which facilitates counting the number of copies generated and extrapolating the number of copies in the material analyzed. Regarding those culture-negative cases, with a cutoff value of two copies, all were also PCR negative at that level, which suggested that the cases that were considered culture-negative do not represent the inability to detect bacteria that are present but represent a minimal bacterial load.

When BRiSK was run, investigators found an interesting torque teno virus (TTV)—a small ubiquitous anellovirus that does not cause inflammatory conditions—that popped up in a number of places.

“Most of the samples from the endophthalmitis cases were positive for this virus,” he said.

TTV was identified on the ocular surface in 22 of 58 ocular swabs, suggesting that the virus entered the eye intraoperatively. However, TTV also could have been present in blood samples.

Interestingly, a separate analysis performed in collaboration with Cecilia Lee, MD, found that TTV was present in 63.6% of samples obtained in a cohort of endophthalmitis cases.

Another small DNA virus, the Merkel cell polyoma virus, also was identified in 25% of samples.

**FUTURE OF SEQUENCING**

DNA sequencing technology is getting smaller and cheaper. Dr. Van Gelder discussed the availability of the hand-held Oxford Nanopore MinION Sequencer that is powered by USB and can generate more than 2 billion base pairs of DNA sequences in 24 hours at a cost of about $90. The device costs less than $1,000.

“Such devices will enable point-of-service diagnostics in the future,” Dr. Van Gelder said. “Deep sequencing will be performed at the bedside or in clinics to determine the pathogenesis of endophthalmitis in time to make therapeutic decisions.”

Molecular diagnostic techniques offer improved sensitivity for detecting pathogenic organisms in postoperative endophthalmitis.

“Deep-sequencing techniques offer further advantages including detection of multiple DNA-based life forms and the information about those forms,” he concluded. “Deep-sequencing techniques have revealed unexpected viruses in culture-negative and culture-positive cases of endophthalmitis. Technologic advances will make next-generation sequencing more accessible to the clinic in the near future.”

Dr. Van Gelder discussed the availability of faster and more accessible techniques including detection of multiple DNA-based life forms and the information about those forms. He concluded that “deep-sequencing techniques have revealed unexpected viruses in culture-negative and culture-positive cases of endophthalmitis.”

Technologic advances will make next-generation sequencing more accessible to the clinic in the near future.”

— Russell Van Gelder, MD, PhD

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This article was adapted from Dr. Van Gelder’s presentation at the 2019 meeting of the American Academy of Ophthalmology. He did not indicate any proprietary interest.
MELANOMA

(Continued from page 1)

system are being developed,” said Dr. Lally, ophthalmologist with the Ocular Oncology Service at Wills Eye Hospital, and assistant professor at Thomas Jefferson University, Philadelphia.

‘We recommend that all specimens be sent for testing and that ophthalmologists work closely with medical oncologists. Based on some mutations found, we are treating patients prophylactically.’

— Sara E. Lally, MD

However, despite these advances, she went on, the genomic landscape of conjunctival melanoma remains obscure, and she pointed out the need for more extensive molecular genetic testing for actionable mutations.

In a study conducted to shed more light on the mysteries surrounding conjunctival melanoma, she and her colleagues analyzed 84 paraffin-embedded samples of conjunctival melanoma for molecular testing from 2007 to 2018 for next-generation sequencing and 73 samples had sufficient tumor cellularity for testing. The BRAF, NRAS, and c-KIT genes were analyzed initially because these were known cutaneous melanoma markers, and later 592 genes were evaluated.

STUDY RESULTS

The average patient age was 61 years; 54% of patients were men. The vast majority (89%), as expected, were Caucasian followed by Asian and Hispanic (5%), and African-American (1%).

The mean basal dimension was 11 millimeters (range, 1-52 millimeters); 61% of patients had completely pigmented lesions. Dr. Lally reported.

The melanoma occurred in all ocular quadrants, with 58% temporally, 44% superiorly, 42% nasally, and 37% inferiorly. When looking anteriorly to posteriorly, the lesions most often were at the limbus in 68% and on the bulbar conjunctiva in 63%; they were less often in the tarsus (20%) and the orbit (7%).

“Our overall, we found 39 mutations, and similar to other reports these included cancer-associated drivers, cutaneous melanoma drivers, and epigenetic regulators,” Dr. Lally said.

The highest frequency mutations found were NF1 (38%), ATRX (31%), BRAF (26%), and NRAS (25%). All of these percentages were similar to the findings of previous studies, except for ATRX (alpha thalassemia/retardation x-linked), which had not been reported previously, but is associated with central nervous system tumors and involved in telomere maintenance, she commented.

Among the samples analyzed, Dr. Lally noted that BRAF presented in three mutations in 19 specimens, 90% of which were missense mutations with V600 differed in the tumor specimens.

No c->t ultraviolet signature mutations were identified among the specimens.

An interesting finding, according to Dr. Lally, was that four patients had choroidal melanoma markers, bap1, gnaq, gna11, and sf3b1. Of these patients, one patient with bap1, ATRX, and NRAS was lost to follow-up; a second patient with bap1 and gnaq11 had metastasis at 8 months and died 2 years later; a third patient with gnaq had a small mass at the limbus and did well with no recurrence until 9 years later when she presented with a nasal lacrimal duct mass; the last patient had sf3b1 and NRAS, which is seen in cutaneous melanoma with more aggressive disease, and 8 months later the cancer metastasized to the liver, which differed from the regional lymph node involvement expected in conjunctival melanoma.

Other mutations of interest were tps3 (13%), set2d (9%), chek2, and fbxw7 (6% each), and kit and pten (2% each). “We recommend that all specimens be sent for testing and that ophthalmologists work closely with medical oncologists. Based on some mutations found, we are treating patients prophylactically,” she said.

TAKE-HOME

» The future of conjunctival melanoma research is gaining a better understanding of the biomarkers of the disease.

E the most common. Six RAS mutations were found in 17 specimens, all of which were missense mutations, the most common of which were Q61R and Q61K, and Q61L also was seen. A wide variety of NF1 mutations were found, and all differed from mutations that had been reported previously. ATRX had 14 mutations in 14 specimens with nonsense, frame shift, and missense mutations seen; all of the mutations differed in the tumor specimens.

No c->t ultraviolet signature mutations were identified among the specimens.

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REFERENCES:


Top questions about MGD treatment options answered

By Cynthia Matossian, MD, FACS; Special to Ophthalmology Times

For patients with meibomian gland dysfunction (MGD), the LipiFlow thermal pulsation system allows physicians to treat patients in office with confidence and efficiency.

Here are some of the questions I am most often asked about LipiFlow by colleagues.

Are these glands too far gone?

It is ideal to treat early in the progression of MGD, in order to preserve stressed but still-working meibomian glands.

But what if a patient presents with advanced gland atrophy or dropout? Is it still worth trying to treat with thermal pulsation therapy?

This is a question I am often asked by colleagues in the hallway at conferences.

In my clinical experience, it is still worthwhile treating if there are even a few functioning meibomian glands remaining. The treatment may be able to help maintain the function of those glands or even restore more glands to functioning status. It was previously thought that gland atrophy is permanent, but Alice Epitropoulos, MD, and Arjun Hura, MD, recently presented a new way to evaluate the meibomian glands using dynamic meibomian imaging.

Will thermal pulsation replace other therapies?

The short answer is no. In most cases, patients should stay on immunomodulators and continue lid health and hygiene measures such as nutritional supplements and warm compresses (I prefer a heated moisturized eye mask to wash warm clothes). These are adjunctive and can help extend the efficacy of the LipiFlow treatment, in my experience.

And for patients with advanced disease, you may want to consider adding more treatments, not fewer, because the etiology of these cases is generally multifactorial. For those with severe blepharitis, I like to do a microblepharoplasty (Blephex) just before thermal pulsation, to get rid of the external biofilm before heating and extracting the meibum.

REFERENCE:

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