Studies target unilateral gene therapy injection

Research finds bilateral BCVA improvement

By Lynda Charters; Reviewed by Patrick Yu-Wai-Man, FRCOphth, FRCPath, BMedSci, MBBS, PhD

DATA FROM TWO clinical studies of Leber’s hereditary optic neuropathy (LHON) showed substantial visual improvements in patients with both disease durations of less than six months and between six months and one year. The improvements resulted from a unilateral injection of a gene therapy vector (GS010) and remarkably, the viral vector seemed to be carried over to the untreated eye.

The mechanism of action for these unexpected results need to be clarified with further experimental work.

LHON is the most common cause of mitochondrial blindness with a minimal prevalence of one in 30,000 individuals in the population. It causes blindness in young adult men with a peak age of onset in third decade of life. It is invariably a bilateral disorder in which the fellow eye becomes affected within six months after disease onset in the first eye. Both eyes are affected simultaneously in about 25%

CONTINUES ON PAGE 17: Injection
Studies target unilateral gene therapy injection

By Cheryl Guttman Krader, BS, Pharm; Reviewed by Burkhard Dick, MD

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Research finds bilateral BCVA improvement

Continues on page 17: Injection
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The first and only once-daily fixed-dose combination of prostaglandin + ROCK inhibitor

IOP: intraocular pressure; ROCK: rho kinase

IMPORTANT SAFETY INFORMATION

Contraindications
None.

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

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

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

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

References:

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

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

Please see brief summary on the adjacent page.

For full Prescribing Information, please visit Rocklatan.com.

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

Visit Rocklatan.com to learn more about this innovative drop for elevated IOP.
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%  
Rx Only  

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

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

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CONTRAINDICATIONS  
None.

WARNINGS AND PRECAUTIONS  

Pigmentation  
Rocklatan® contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, pterional tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Beyond 5 years the effects of increased pigmentation are not known.

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

Eyelash Changes  
Rocklatan® contains latanoprost which may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation  
Rocklatan® contains latanoprost which should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because it may exacerbate inflammation...

Macular Edema  
Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. Rocklatan® should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

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

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

Use with Contact Lenses  
Contact lenses should be removed prior to the administration of Rocklatan® and may be reinserted 15 minutes after administration.

ADVERSE REACTIONS  

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

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

Other adverse reactions that have been reported with the individual components and not listed above include:

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

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

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

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

USE IN SPECIFIC POPULATIONS  

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

Animal Data  
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥20.3 mg/kg/day (126-fold the plasma exposure at the RHOD, based on Cmax). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on Cmax).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on Cmax). Malformations were observed at ≥2.5 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on Cmax), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on Cmax).

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

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

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

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

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

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

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

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

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Imaging

9 OCT ARTIFACTS AND PITFALLS: IN THE EYE OF THE BEHOLDER
Scans correlate structure with function of the optic nerve in glaucoma patients.

10 MAKING THE MOST OF IMAGING IN PEDIATRIC PATIENTS
Technologies determine nature of anatomic abnormalities, level of severity.

Surgery

1 IMPROVING OUTCOMES OF CATARACT SURGERY
Multiple innovations target postoperative refractive adjustment.

12 ACCURATE DATA KEY FOR PLANNING TORIC IOL SURGERY
Information can help physicians optimize astigmatism outcomes in patients.

13 WAVEFRONT-GUIDED PRK OFFERING ‘SUPER VISION’ FOR PATIENTS
Military study data drives approval of procedure in the United States.

Gene Therapy

1 STUDIES TARGET UNILATERAL GENE THERAPY INJECTION
Research finds bilateral BCVA improvement with procedure for Leber’s hereditary optic neuropathy (LHON).

16 BLAZING A NEW TRAIL IN GENE THERAPY FOR RETINAL DISEASE
Achievements and trends highlight promise for new treatment options.

Device Technology

20 RESEARCHERS REACHING FOR THE STARS TO CURE PRESBYOPIA
Simulator allows patients to ‘test’ anticipated postop vision results prior to surgery.

21 CHANGING FOCUS OF ACCOMMODATING IOLs NOW REACHING A NEW LEVEL
Optic position changes to shift power from distance to near and back.

22 PULSING OR PROBING FOR MGD: HOW CURRENT DEVICES COMPARE
Current data offers physicians no clear conclusion about any particular technology.

Therapeutics

23 BIOENGINEERING PUTS FOCUS ON RETINAL DEGENERATION
Varied approaches are giving physicians vision-restoring options for patients.

24 RHo KINASE INHIBITORS: FILLING A GAP IN GLAUCOMA TREATMENT
Latest options include mechanism of action on trabecular meshwork without side effects.

Clinical Diagnosis

27 PEARLS FOR MANAGEMENT OF OCULAR CICATRICAL DISEASE
Controlling inflammation key to successful treatment strategy for patients.

28 CONNECT THE DOTS: DIAGNOSING, MANAGING MULTIFOCAL CHOROIDITIDES
Amid multiple prognoses, early treatment of the white dot syndromes using steroids and immunosuppression therapy is key to success.
Gene therapy driving innovation

MIKE HENNESSY SR., Chairman and founder of Ophthalmology Times’ parent company, MJH Life Sciences

ON THE COVER: Of this issue, we look at gene therapy research that is uncovering key patient benefits. Gene therapy is a promising treatment strategy for Leber’s hereditary optic neuropathy (LHON). Patrick Yu-Wai-Man, FRCSophth, FRCPath, BMedSci, MBBS, PhD, discusses how data from two clinical studies of LHON showed substantial visual improvements in patients with both disease durations of less than six months and between six months and one year. This could prove to be of particular interest to ophthalmologists.

Our cover highlights a discussion with Burkhard Dick, MD, PhD, who details several approaches to improving outcomes of cataract surgery, including a look at some available and emerging technologies.

Inside this month’s issue, we kick things off with our special section focusing on imaging. Richard K. Lee, MD, PhD, tells us that attention to detail is key when reviewing optic coherence tomography (OCT) images to get a real picture of what is occurring in the eye. He also notes that OCT can assist ophthalmologists in the diagnosis and treatment of glaucoma in patients.

In surgery, we look at the importance of data when planning toric IOL procedures. Noel A. Alpins, MD, explains that this can be key to optimizing astigmatism outcomes in patients. He points out that outcomes of can be improved when the planning considers the flattening effect of the phacoemulsification incision rather than the surgically induced astigmatism vector and uses total corneal topographic astigmatism or measured total corneal power instead of an estimated value.

We also hear from Elizabeth Hofmeister, MD, a U.S. Navy captain and chairwoman of ophthalmology at the Naval Medical Center, San Diego. She was the lead investigator in a prospective, multicenter study that evaluated 167 myopic patients undergoing bilateral PRK with an excimer laser guided by a new wavefront aberrometer. She notes that with some relatively simple precautions, wavefront-guided PRK allows surgeons to finally achieve results of vision that is better than 20/20 for patients.

Our gene therapy coverage also includes an interesting look at how gene therapy to treat retinal degeneration is thriving. According to Jean Bennett, MD, PhD, dozens of centers around the world are studying subretinal and intravitreal gene delivery, and more than 1,000 centers around the world are studying subretinal and intravitreal gene delivery, and more than 1,000 patients are enrolled in trials. We’ve seen advances over the past three decades and that innovation continues today.

In device technology, we focus on a visor that enables patients to test their expected postoperative results before surgery. A visual simulator provides patients the experience of vision with multifocal IOLs before actual implantation of the device, helping to manage patients’ expectations.

The area of therapeutic continues to offer interesting options for ophthalmologists, and in this issue Mark S. Humayun, MD, PhD, discusses bioengineering strategies that can help overcome challenges to achieving success with advanced implants aiming to bioengineer the macula.

Irmgard Behlau, MD, tells us that approaches have been developed to treat endophthalmitis, including topical and systemic drugs and periocular and intravitreal injections. The noninvasive methods of topical and systemic means of delivery are the goals because of their lack of invasiveness. With injections, there is always the risk of development of endophthalmitis. We will explore some of the therapeutic approaches.

On the clinical diagnosis docket, Clara C. Chan, MD, FRCSc, FACS, offers some pearls for managing ocular cicatricial disease. She notes that it requires a step-wise approach to secure the best results. The first step is keeping the inflammation under control. Without that control, the patient can slide down a path filled with hurdles to improving ocular health.

We also discuss successful treatment of the white dot syndromes is more readily achieved with early treatment using steroids and immunosuppression therapy. The various multifocal choroidopathies differ in course, prognosis, and treatment. While the prognoses do differ, they are hopeful with early treatment in most cases.

What’s Trending
See what the ophthalmic community is reading on OphthalmologyTimes.com

1 Simulator helps patients ‘see’ with multifocal IOLs before implantation
OphthalmologyTimes.com/MultifocalIOLs

2 Hypersonic vitrectomy: Exploring novel way of vitreous removal
OphthalmologyTimes.com/HypersonicVitrectomy

3 Dexamethasone insert reduces postsurgery burden
OphthalmologyTimes.com/DexamethasonePostSurgery

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Video
Helga Pizio MD, FACS, shares the results of a study using data from Bausch + Lomb’s eyeTELLIGENCE platform titled “Energy-Fluid Metrics Analysis of Patients Undergoing Vacuum-Based Phacoemulsification From Cloud-Based Database” during AAO 2019. Go to OphthalmologyTimes.com/AAO2019/HelgaPizio
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Doctors, nurses and medical records

Professionals can find common ground with paperwork crunch

By Peter J. McDonnell, MD

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

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BROKEN SYSTEM

As suggested by its title, the article posits that physicians and nurses don’t get along in an American healthcare system described as “broken, wasteful, inhuman, expensive, deadly.” They assert that “too often, each profession sees the other as fighting separate battles, and sometimes against each other.

Doctors blame nurses, and vice versa, for the failings of a system that punishes us all, and our patients. Physicians earn more than nurses and have much higher status in the medical hierarchy, which can lead to resentment from nurses when that higher status is abused. It noted that “the gendered history of both professions also contributes to a view of nurses as fundamentally subordinate to physicians.”

The authors go on to say that “nurses and physicians must come together” to oppose a shared unfair burden: excessive demands for documentation in electronic medical records. Citing a report from the National Academy of Medicine that says the average doctor and nurse are spending 50% of the workday documenting in the computer, they feel that the two professions should speak with one voice to address this problem and the associated burnout.

“Doctors would be wise to let nurses take the lead” say the authors, because nurses have strong unions and doctors don’t. “The Service Employees International Union and National Nurses United represent nurses all over the United States and in general are good at getting their demands met.”

I found myself having a couple of reactions to this argument. My first reaction may relate to my being an ophthalmologist, or it might relate to the culture of the institution where I work, but I have never heard one of my physician colleagues blame nurses for any ills of our U.S. healthcare system.

DEDICATION OF NURSES

Rather, I frequently hear praise for the skill, dedication and caring exhibited by our nurses (and I am told this in private conversations when there is no ulterior reason that might be attributed). And that goodwill is reciprocated, as far as I can tell. Each of us can have a bad day, perhaps, when we get a little cranky, but my experience tells me that the typical doctor-nurse relationship that I observe is one of mutual respect and admiration, and nothing like the finger pointing and blaming for healthcare ills described in the Times editorial.

But I do agree with the thesis that the burden of documentation has become excessive. The authors state that the model we should move toward is that of the Veterans Administration hospitals, where we are told the clinicians like their electronic records system. The reason given for this is that “billing concerns don’t shape the records at government-run V.A. hospitals. They document only what’s necessarily deliver better care.”

I would love to know what you, dear Ophthalmology Times readers, think about this issue. Do you ever find yourself or hear physician colleagues blaming nurses for the ills of the U.S. healthcare system? And do those of you who work in the Veterans Administration system actually like your electronic records and think it should be the model going forward?

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OCT ARTIFACTS AND PITFALLS: IN THE EYE OF THE BEHOLDER

Scans correlate structure with function of the optic nerve in glaucoma patients

By Lynda Charters; Reviewed by Richard K. Lee, MD, PhD

D iagnosing and managing glaucoma now commonly involves the aid of optical coherence tomography (OCT) scans to correlate structure with function of the optic nerve. Sounds simple enough.

For example, a patient with an inferior optic nerve head notch has a superior visual field defect that can then be correlated and quantified on the OCT scans and confirm that there really is loss of the nerve fiber layer, according to Richard K. Lee, MD, PhD, associate professor and the Walter G. Ross Distinguished Chair in Ophthalmology at the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami.

Clinicians should not be concerned only with structure to follow or identify glaucomatous disease. He noted that in the Ocular Hypertension Treatment Study (Ophthalmology. 2006;113:1603-12), the optic nerve head (ONH) showed the first signs of disease progression in almost 60% of patients. In a third of the patients the first sign of glaucoma development was visual field deterioration. Both should be followed. Optic nerve dysfunction with concomitant cupping of the ONH was observed in only 7% of patients.

**NOTHING IS PERFECT**

No matter how much a perfect instrument is desired, OCT machines have their shortcomings.

“Clinicians can see ONH hemorrhages, pallor, edema, peripapillary crescents white, black, or grey, or other features of the optic nerve anatomy that cannot be observed in or identified by OCT,” Dr. Lee said. “There is no reliable information at all in eyes with high myopia where the OCT signal strength is so poor that no imaging is possible.”

OCT can be invaluable when tracking glaucoma progression. If physicians rely only on the green color coding, and don’t look more closely, they can easily miss the fact that the nerve fiber layer (NFL) may be continuously becoming thinner and thinner. The OCT printout tells the clinician that the NFL thickness is in the normal range relative to the normative database, but the clinician may miss the thickness issue.

Evaluation of the VF in such a patient may show continued progression of a glaucomatous VF defect that can happen despite aggressive medical therapy.

“This patient could be seen as normal, but functionally getting much worse,” Dr. Lee commented. Physicians used to review all the data manually. OCT can provide all of this information with an automated comparison of current to prior OCTs to determine if there is change which, Dr. Lee believes, should be reviewed for all patients on a regular basis.

“The lesson here is that in some eyes no signal can be obtained, and the eye can be absent and a normal signal can be obtained,” he explained. “The caveat is that clinicians must look closely at their scans and correlated to the clinical examination. The fact that there were no OCT NFL scan results should tell the ophthalmologist that something is wrong.”

A number of variables affect OCT instruments that are machine-, operator-, and patient-dependent.

“We always obtain duplicate or triplicate OCT scans or more at the same sittings for comparisons of minute details among the scans,” Dr. Lee said. Clinicians should check the signal strength and segmentation, review the right and left eye and superior and inferior NFL density butterfly pattern and the average NFL thickness, and look for asymmetry and progression of the NFL loss.
Making the most of imaging in examination of pediatric patients

Technologies help determine nature of anatomic abnormalities, level of severity

By Lynda Charters; Reviewed by Phoebe D. Lenhart, MD

CONDUCTING EXAMINATIONS IN uncooperative patients is challenging, especially in children. However, anterior-segment optical coherence tomography (AS-OCT), ultrasound biomicroscopy (UBM), and corneal topography have made that task easier in the pediatric population.

These technologies are helpful in children because they can determine the nature or level of anatomic abnormalities and the level of severity, facilitate following a pathology over time, which aids in surgical decision making and formulating the optimal management plan, and shed light on the prognostic implications, according to Phoebe D. Lenhart, MD, associate professor of ophthalmology, Emory University School of Medicine, Emory Eye Center, Atlanta.

AS-OCT
She described the case of a 12-year-old boy with long hair that continuously hit him in the eye, causing a large corneal scar. AS-OCT visualized the presence of a central nodule with a very irregular surface that involved the anterior third to half of the cornea, which resulted in the diagnosis of a large Salzmann’s nodule. AS-OCT in this case also aided the patient’s visual rehabilitation by facilitating the customized design of a scleral contact lens that incorporated multiple OCT data points and ensured the safety of the cornea.

Orthokeratology patients can also benefit from the use of AS-OCT, because the technology can confirm how well the lens fits. Orthokeratology lenses have a reverse geometry to conventional contact lenses and provide apical flattening and midperipheral corneal steepening to correct the peripheral hyperopic retinal defocus.

“The lens effectively negates the stimulus for axial elongation,” Dr. Lenhart said.

In the youngest patients and patients who are developmentally delayed, AS-OCT can also be beneficial in the operating room with the patient under anesthesia. She demonstrated that in an early attempt to use the technology, she was able to obtain a great deal of information about the depth of a pathology, which in this case were progressive corneal keloid lesions in a 1-year-old boy.

The technology also helps the surgeon gauge incisional depths as in a patient with limbal dermoid.

“While UBM is not the most current technology, in some cases it is the most useful in cases of anterior segment dysgenesis or complete corneal opacification, because it provides visualization when visualization is otherwise impossible,” she said.

Work by Nischal et al. (Br J Ophthalmol 2002;86:62–69, UBM) has even demonstrated errors in clinical phenotyping in almost half of cases of anterior segment dysgenesis. Cases that were misdiagnosed as sclerocornea actually had high-frequency ultrasound characteristics of Peters anomaly.

Knowledge about whether a patient has iridocorneal or lenticulocorneal adhesions may make the difference in the success rates of keratoplasty, which differs markedly according to type of anterior segment dysgenesis, she said. The success of grafts with only iridocorneal adhesions can be as high as 80% to 90%, while success rates are much lower in eyes with lenticulocorneal adhesions.

CORNEAL TOPOGRAPHY
In most cases, keratoconus can be easily diagnosed. In some cases, it can be a challenge. Dr. Lenhart recounted the case of an 11-year-old boy with acute hydrops in the right eye. AS-OCT showed severe corneal thinning and bowing in the left eye.

In other cases, the diagnosis is more difficult because the cornea in early keratoconus can appear normal during a slit-lamp examination.

“Take-home ➢ Imaging technologies can be used in tandem with other clinical findings to design the best plan possible for each patient.”

CONCLUSION
“All of these technologies should be used together with other clinical findings to design the best plan possible for each patient. Delays in diagnosis and treatment can lead to amblyopia in younger children and visual loss,” she concluded.

Dr. Lenhart said she likes to use the Pentacam (Oculus) because it allows images to be obtained quickly in young or uncooperative children. The instrument provides an axial curvature map, anterior and posterior float map, and a pachymetry map, all of which show the corneal peaks and troughs using color coding compared with normative databases. Using the information garnered from both the corneal topography and the clinical examination, a diagnosis of keratoconus can be reached and the degree of keratoconus can be differentiated in the same patient, because different degrees of severity will determine appropriate treatment.

In one patient, a 14-year-old boy, the axial curvature map showed severe paracentral steepening in the right eye (flat and steep keratometries, 65 D and 67 D, respectively).

Pachymetry showed central corneal thickness of 415 μm, which was thin in the area of steepening. The anterior and posterior float maps showed paracentral bulges suggesting elevation. This patient had advanced keratoconus. He was referred for cross-linking in the left eye but underwent a corneal transplant in the right eye that was more severely affected.

In another case, in which the degree of keratoconus differed between the eyes, the right eye required penetrating keratoplasty for visual rehabilitation, and the left eye was treated with cross-linking. AS-OCT performed after the keratoplasty to custom fit a scleral contact lens showed good clearance between the lens and the anterior corneal surface.

This article is based on Dr. Lenhart’s presentation at the American Academy of Ophthalmology’s 2019 annual meeting. Dr. Lenhart has no financial interests related to the topic of this report. Some of the imaging modalities used in children are off-label.
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Accurate data key for planning toric IOL surgery

Information can help physicians optimize astigmatism outcomes in patients

By Cheryl Guttman Krader, BS, Pharm; Reviewed by Noel A. Alpins, MD

OUTCOMES OF TORIC IOL surgery can be improved when the planning considers the flattening effect (FE) of the phacoemulsification incision rather than the surgically induced astigmatism vector (SIA) and uses total corneal topographic astigmatism (CorT Total) or measured total corneal power (TCP) instead of an estimated value, according to Noel A. Alpins, MD.

“The incisional flattening effect (FE) is more accurate than the surgically induced astigmatism vector (SIA) and CorT Total or measured TCP is more accurate than estimated total keratometry values,” said Dr. Alpins, medical director, NewVision Clinics, and clinical professor of ophthalmology, Melbourne University, Melbourne, Australia.

FLATTENING EFFECT

Dr. Alpins explained that the flattening effect of the phaco incision, which is calculated from the analysis of previous surgeries, should be used rather than the SIA because the flattening effect represents the astigmatic reduction effect at the site of the incision.

In contrast, the SIA is composed of a flattening/steepeening component, which is the effect in the direction of the incision, as well as a torque component, which rotates the astigmatism but does not reduce the astigmatism.

“When there is any amount of SIA that is off-axis from the incision, the SIA is an overstatement of the amount of change occurring at the incision site,” Dr. Alpins said.

Research showing how SIA can vary considerably depending on various factors also highlights the potential pitfalls of using a manufacturer-recommended SIA of 0.10 D as a default value for toric IOL power calculations.

For example, the astigmatically active incision is most active when operating on the steep meridian and more astigmatically neutral when operating on the flat meridian.1 In addition, it has been shown that the magnitude of the SIA varies depending on the amount of astigmatism present, increasing by 0.37 D for every 1 D increase in astigmatism.2

Citing results from a study he conducted analyzing data from operating on 1,300 eyes of 650 patients, Dr. Alpins demonstrated that the flattening effect of his 2.2-mm incision differed significantly between right and left eyes and was three times greater than a manufacturer’s recommendation to use an SIA value of 0.10 D for incisions ≤2.50 mm.

In his study, Dr. Alpins determined that the SIA averaged 0.64 D and the mean flattening effect was around 0.3 D.1

MEASURING ASTIGMATISM

CorT Total is a vectorially calculated parameter derived from an average over a wide annular region on the cornea that incorporates anterior and posterior corneal astigmatism and corresponds better in magnitude and orientation to the refractive cylinder than simulated K (Sim K), manual keratometry and autokeratometry, regardless of corneal regularity.

“The simulated keratometry value displayed by the corneal topography maps is derived from data within a narrow 3.0 mm zone, which can have some variability when there is irregularity,” Dr. Alpins said.

“CorT Total is derived from a wider region,” he said. “Using data from all of the rings and taking a vectorial average washes out the error introduced by irregularity in any one ring, so variability is low.”

In a recent study, Dr. Alpins and colleagues reported that CorT Total is a reliable measure that corresponded with the manifest refractive cylinder as well as the total corneal power measures from two Scheimpflug tomographers and better than those of a third [Alpins NA, et al. Cornea. 2019; Oct 9 Epub ahead of print].3

TAKE-HOME

The use of accurate data for planning toric IOL surgery is the key to optimizing astigmatism outcomes.

REFERENCES


O nline Calculators

Members of the International Society of Refractive Surgery have free online access (www.isrs.org) to a series of calculators for astigmatism analysis, Vector Planning and toric IOL calculations. The calculators include the ASSORT Group Analysis Calculator that uses the Alpins Method to generate group analyses and the standard Journal of Refractive Surgery graphs. It has options for analyzing changes in refractive cylinder, changes in corneal astigmatism, and outcomes of toric IOL implantation.

The ASSORT Toric IOL calculator is another feature. Its inputs include anterior corneal power or Corf’ anterior and either CorT total or TCP from a tomographer, and it generates the expected refractive outcomes for any available toric implant using different combinations of sphere and cylinder so that surgeons can select a lens that is predicted to result in a spherocylinder that is closest to 0.

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Wavefront-guided PRK offering ‘super vision’ for patients

Military research data driving approval of procedure in United States

By Jan Beiting

THE U.S. ARMY, Navy and Air Force together perform between 30,000 and 40,000 laser vision correction procedures each year, about three-quarters of which are surface ablation procedures. As a result, there is a strong interest from the U.S. military in the continued development of advanced refractive technology for PRK.

Elizabeth Hofmeister, MD, a U.S. Navy captain and chairwoman of ophthalmology at the Naval Medical Center, San Diego, was the lead investigator in a prospective, multicenter study that evaluated 167 myopic patients undergoing bilateral PRK with the Star S4 IR excimer laser guided by a new wavefront aberrometer, the iDesign Refractive Studio (both from Johnson + Johnson Vision).

“The patients in our study were younger (mean age 26.6, range 19-47) and more likely to be male (68%) than in a typical civilian refractive surgery population,” Dr. Hofmeister said.

To be eligible for the study, patients had to have healthy eyes correctible to 20/20 or better before surgery. They could have up to -10 D of iDesign wavefront refraction spherical equivalent (iDSE), with sphere up to -8.00 D and cylinder up to -4.00 D. There had to be a close match between the manifest and wavefront refractions, with < 0.625 D difference between the two, and < 0.5 D difference in cylinder.

In the study, the epithelium was removed with an Amoils brush, without alcohol. Mitomycin C 0.01% was applied for 15 seconds at the end of the procedure and then rinsed copiously with chilled balanced salt solution (BSS).

“To mitigate discomfort after surgery,” Dr. Hofmeister said, “a bandage contact lens was applied, and patients were given oral NSAIDs as needed, a short course of oral antibiotics, if needed, and were authorized to use dilute topical tetracaine every two hours, up to six times per day. Any remaining tetracaine solution had to be returned after the one-week follow-up visit.”

RESULTS
Preoperatively, the mean iDSE was -4.09 ± 1.97 D (range -8.99 to -0.64). The mean sphere was -3.56 ± 1.96 D and the mean cylinder was -1.05 ± 0.83 D.

“At six months postoperatively, monocular UCVA was impressive, with most eyes seeing better than 20/20,” she said. “The accuracy of the correction was also excellent, with 85.4% of eyes within 0.5 D of intended correction; 92.2% had a manifest cylinder refraction within 0.5 D. Additionally, the intended-versus-achieved slope was 0.951, or very close to the ideal of 1.00.” Refractive stability was demonstrated by six months.

Patient satisfaction was very high, with 98.8% saying they were “completely” or “very” satisfied overall and without wearing glasses or contact lenses. Nearly 90% said they never wear glasses or contact lenses. No subjects said they were “very” or “extremely” bothered by halo, glare or starburst and more than 96% said they either did not experience night vision symptoms at all or were not or only slightly bothered by them. Complaints of night vision symptoms were slightly improved postop compared to preop.

“We found that the procedure was quite safe, with less than 1% of eyes experiencing any adverse event,” said Dr. Hofmeister. There was one eye with corneal haze and a >2 line loss of vision (0.3%). Overall, the rate of corneal haze was 0.9%. The rates of corneal infiltrate and corneal erosion were each 0.6%.

DISCUSSION
Certainly, wavefront-guided PRK was already being performed on an off-label basis in both civilian and military settings,” Dr. Hofmeister explained. “It is particularly important to the military community to have an approved WFG surface procedure, given the high volume of PRK procedures we do every year.”

Dr. Hofmeister further explained that PRK remains quite popular due to concerns about flap safety, even though studies have shown that the rate of flap dislocations in the military is very low.

“Additionally, because our patients tend to be quite young, military surgeons are more conservative about performing surgery at the young age.”

Ophthalmology Times

Monocular UCVA at Six Months

<table>
<thead>
<tr>
<th>Monocular UCVA</th>
<th>20/16 or better</th>
<th>20/20 or better</th>
<th>20/40 or better</th>
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<td>91.5%</td>
<td>99.4%</td>
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(FIGURE 1) Results proved to be beneficial for patients.

(Chart courtesy of Elizabeth Hofmeister, MD)

Wavefront-guided PRK

<table>
<thead>
<tr>
<th>Night Vision Symptoms at Six Months</th>
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<td>HALO</td>
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<td>GLARE</td>
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<td>96.3%</td>
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(FIGURE 2) Patients reported few symptoms.

(Chart courtesy of Elizabeth Hofmeister, MD)

Take-home

➢ With some relatively simple precautions, wavefront-guided PRK allows surgeons to finally achieve results of vision that is better than 20/20 for patients.

Continues on page 14: PRK
CATARACT

(Continued from page 1)

“A vast amount of experience underscores the value of this three-piece silicone lens whose refractive power can be changed within a few weeks after cataract surgery by specifically targeted UV irradiation,” he said. “I consider the light-adjustable lens a great option to improve refractive outcomes and advance patient care.”

The upgraded light-adjustable lens platform features added UV protection, is implanted with a proprietary injector that allows introduction through incisions ≤ (≤) 2.75 mm, and is adjusted with a new light delivery device. This offers improved ergonomics, a 10-fold reduction in retinal UV irradiance, and new optical patterns.

“The new platform allows for earlier noninvasive post-implantation adjustment and less lock-ins, and it can create an extended depth of focus pattern, induce negative asphericity, and be used to design individually adjustable mini-monovision,” Dr. Dick said.

The safety and performance of the new light-adjustable lens was investigated in a multicenter European study that enrolled 100 eyes of 50 patients with 0.5 to 3 D of preop keratometric astigmatism. The results demonstrated the safety and efficacy of the upgraded light-adjustable lens technology, Dr. Dick said.

“More than 70% of eyes achieved 20/20 or better UCVA, which represents a twofold improvement over the outcomes achieved with toric IOLs, and the accuracy to target refraction for spherical equivalent and cylinder was exceptionally high, matching LASIK outcomes,” he pointed out.

“In addition, the incidence of both glare and halo were very low.”

**MULTICOMPONENT ADJUSTABLE IOLs**

Refractive adjustment with multicomponent adjustable IOLs is achieved by exchanging a front optic with a new component that corrects refractive error or better serves the patient’s vision goals. The two available technologies differ in design.

The PreciSight multicomponent IOL is a dual optic platform that is implanted into the capsular bag. In contrast, the Harmoni Modular IOL uses a scaffold that is implanted into the bag and a front exchangeable optic.

“My personal opinion is that because the multicomponent IOLs require a secondary procedure for power adjustment, they are best considered in situations where there is an increased likelihood of refractive change, such as in cases of pediatric cataract, progressive corneal pathology, or with vitreoretinal tamponade,” Dr. Dick said.

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PRK

(Continued from page 13)
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any topographic abnormalities with potential for later ectatic disease,” she said.

Military patients, she said, have the advantage of knowing what to expect (because many of their colleagues have had PRK) and also have the ability to take a week off work without negative consequences.

“We were truly surprised by how good the visual acuity outcomes in this study were—among the best every reported for corneal refractive surgery,” said Dr. Hofmeister.

Dr. Hofmeister also explained that, while the excimer laser is highly accurate, that has been the case for many years.

“What is new with this procedure is the high degree of accuracy of the wavefront aberrometer in measuring the refractive error and, in particular, the cylinder,” she said. “In my opinion, precise correction of low levels of astigmatism may make the difference between 20/20 and 20/16 vision.”

Dr. Hofmeister and other surgeons involved in the study also counseled that it is very important that surgeons perform a good manifest and cycloplegic refraction, ensure that patients (especially young ones) are not accommodating, and verify that the iDesign and manifest refractions are similar to one another, within the parameters recommended by the manufacturer. In older patients and former contact lens wearers, care should be taken to ensure good ocular surface quality.

“Optimizing acuity and quality of vision is important for any refractive surgery patient, and this is especially true in a military setting in which demanding visual environments, including low light, low contrast, and fast-moving targets, are common,” said Dr. Hofmeister.

“With the relatively simple precautions outlined above, wavefront-guided PRK with the iDesign system allows us to finally achieve the routine ‘super vision’ (better than 20/20) that has long been our goal.”

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**TAKE-HOME**

- A variety of approaches are commercially available or in development that allow refractive adjustment after cataract surgery, including changes in sphere, cylinder, asphericity, and multifocality.

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**LASER-INDUCED REFRACTIVE INDEX ANGEBUS**

Laser-induced refractive index change (LIRIC) is caused by multiphoton absorption of ultrashort laser pulses and can be performed in silicone, hydrogel, or dye-doped polymers but also in the cornea.

Clerio Vision, one company developing LIRIC technology, is focusing on the development of a device for refractive index modification in the cornea that could supersede LASIK and is the first company to demonstrate LIRIC of a living human cornea.

The company is also working on a benchtop customization device for contact lenses and investigating modification of IOL materials, according to Dr. Dick.

Perfect Lens is another company working in the LIRIC space. It focuses on developing a device for in vivo IOL adjustment.

So far, the company has demonstrated IOL power adjustment in live rabbit eyes and the feasibility of adding or canceling IOL multifocality in a model eye.

Medicem is designing IOL material optimized for modification by a femtosecond laser and a device for in vivo IOL modification. To date it has found a material suitable for refractive index shaping that is expected to have potential for relatively high power change.

LicriEye (Merck) currently is developing polymers containing coumarin side groups to enable photo-induced adjustment of LIRIC. Its work is in an early stage of development.

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This article is based on Dr. Dick’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Dick is a consultant to ReSight.

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**ELIZABETH HOFMEISTER, MD**

p: 619/532-7272

Dr. Hofmeister has no financial interests to disclose related to this article.
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**Blazing a new trail in gene therapy for retinal disease**

Achievements, trends highlighting promise for new treatment options

*By Lynda Charters; Reviewed by Jean Bennett, MD, PhD*

When considering accomplishments recorded in the arena of gene therapy, the “firsts” are impressive. Voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) was the first gene therapy to receive FDA approval and EU approval to treat an inherited disease—Leber’s congenital amaurosis (LCA), an autosomal recessive blindness—in the United States and Europe.

The clinical trial of voretigene neparvovec-rzyl was the first to enroll pediatric subjects with a non-lethal disease. The drug, according to Jean Bennett, MD, PhD, was the first to develop a path for the development of genetic treatments for blindness and provided motivation for ophthalmologists and insurers to carry out genetic testing.

Dr. Bennett is director of the Center for Advanced Retinal and Ocular Therapeutics, professor of ophthalmology and professor of Cell and Development Biology, University of Pennsylvania Perelman School of Medicine, Philadelphia.

Over the previous three decades, several vehicles to deliver gene therapy have been tested; the one that stood out in many studies was the adeno-associated virus (AAV), a single-strand virus that is not disease-causing in animals or humans and can infect postmitotic neurons and dividing cells, Dr. Bennett said.

When injected by subretinal injection, the AAV vector delivers the promoter and the gene under study, and this blueprint ultimately makes its way to the nucleus as a stable episome.

“There has been huge progress over the years,” she said. “There are now 271 genes identified that, upon mutation, cause retinal degeneration.”

RPE65 mutations cause progressive retinal degeneration beginning with early-onset night blindness and nystagmus among other symptoms in the dogs and children with the naturally occurring disease.

The effects of the gene therapy were readily apparent in the dog model of LCA. Before injection, the dogs had no pupillary light reflex when the eye was illuminated; after treatment, there was a brisk pupillary light reflex and the dogs were able to negotiate their way around a room without bumping into objects, which was impossible previously.

“A 38-gauge cannula is used to deliver the reagent, which causes a localized retinal detachment that serves to deliver the AAV to the targeted cells.”

Children who were candidates for treatment also attempted to negotiate their way around a mobility course before treatment; after treatment they moved through the course with no problem. This experiment was fine-tuned and validated in a separate study, Dr. Bennett recounted, and later used as the primary outcome in a phase III trial.

“The outcome measure showed robust statistical improvement and led to the approval of voretigene neparvovec-rzyl as a drug for LCA,” she said.

Individuals treated with voretigene neparvovec-rzyl showed marked improvements in light sensitivity, visual fields, and visual acuity. Dr. Bennett described one young man, a singer, who prior to treatment, was led onto the stage to perform and was unable to interact with and make eye contact with the audience. Following treatment, he went on to develop a singing career, won a segment on the television talent show, “America’s Got Talent!” and is progressing further in composing and performing.

**Trends in gene therapy**

Having an animal model for LCA was serendipitous. But what happens when no such model is available? Dr. Bennett noted there is no animal model.

“We can take advantage of induced pluripotent stem cells, grow them in a dish, dedifferentiate them, and then differentiate them along a retinal-specific path, and develop a gene therapy that is tested in a dish,” she said.

If that effort is successful, the next step is safety studies in wildtype animals and a gene therapy clinical trial.

Dr. Bennett and colleagues followed this path for choroideremia and ultimately conducted a clinical trial for the disease. Other groups are also following their lead.

What happens when a disease is not autosomal recessive or X-linked recessive?

“With diseases that are autosomal dominant, where there are gain-of-function mutations, this is a lot more challenging and may require removal of the disease-causing gene and addition of a new one or gene editing,” according to Dr. Bennett.

Another approach may be by manipulating the mutant gene sequence. Editas Medical is currently enrolling patients in a clinical trial of LCA10 using this process.

In order to start treating the numerous other retinal degenerations, Dr. Bennett pointed out the need to start targeting pathways.

“We can potentially deliver neurotrophic factors to delay apoptotic cell death,” she said. Some research groups are investigating this avenue.

Pathways for wet age-related macular degeneration also can be targeted. RGX-314 developed by Regen-bio is a one-time subretinal anti-vascular endothelial growth factor (VEGF) gene delivery treatment that may possibly eliminate the need for frequent administration of anti-VEGF injections.

Another ambitious project involves optogenetic therapy that may possibly treat end-stage retinal diseases in patients with no viable photoreceptors.

Amid these developments, Dr. Bennett said the future of gene therapy is very bright.

“Gene therapy is alive and well. Dozens of centers around the world are studying subretinal and intravitreal gene delivery, and more than 1,000 patients are enrolled in trials.”

**Timeline for wet age-related macular degeneration**

- **2007**: Developed a one-time subretinal anti-VEGF drug delivery treatment that may possibly eliminate the need for frequent administration of anti-VEGF injections.

**The Backstory**

The clear documented improvement in vision in both the dogs and then the children with RPE65 mutations paved a clear path to FDA approval of the drug to treat LCA.
of patients, according to Patrick Yu-Wai-Man, FR-COphth, FRCPath, BMedSci, MBBS, PhD, an academic neuro-ophthalmologist with faculty positions at the University of Cambridge, Moorfields Eye Hospital, and the UCL Institute of Ophthalmology, in the UK.

Three primary mutations within the mitochondrial genome cause about 90% of cases worldwide, namely, m.3460G>A, m.11778G>A and m.14484T>C, with m.11778G>A being the most common mutation by far, accounting for over 70% of those affected with LHON. Unfortunately, most affected patients remain legally blind with vision worse than 1.3 logarithm of the minimum angle of resolution (logMAR) or 3/60 in Snellen equivalent.

Given the poor prognosis, there is an urgent clinical need to identify effective treatments for this blinding optic nerve disease.

**TREATMENT**

“Gene therapy is obviously a very attractive treatment option, because the underlying pathophysiology is due to insufficient amount of the wild-type protein,” Dr. Yu-Wai-Man said. “Therefore, if the defective gene is replaced, we should be able to rescue the retinal ganglion cells, preserving function and improving the visual prognosis.”

He described the principles of allotopic gene expression that involves inserting the mitochondrial gene of interest, in this case MTND4, into the nuclear genome with a modified viral vector. The wild-type protein produced has a specific mitochondrial targeting sequence that directs it to be imported into the mitochondrial compartment.

The use of an intravitreal injection is a big advantage for this treatment approach as it is a relatively straightforward procedure that provides direct access to the inner retina. Previous preclinical work indicates that allotopic expression is able to rescue the retinal ganglion cells from the deleterious effects of the m.11778G>A mutation.

**CLINICAL TRIALS**

RESCUE and REVERSE are two studies sponsored by GenSight Biologics. The RESCUE study included 39 subjects with the m.11778G>A mutation who have had the disease for 180 days or less. The REVERSE study included 37 subjects who had lost vision for 181 to 365 days. In both studies, one eye was treated with the gene therapy vector (GS010) and the contralateral eye received a sham treatment.

The primary end point of the RESCUE study was the difference between the GS010-treated and sham-treated eyes at 48 weeks, with the hope of finding a difference between the eyes of 15 or more letters on the ETDRS chart. Other parameters of visual function were assessed, including optical coherence tomography imaging and patient-reported quality-of-life measures.

Among the 39 patients (31 men) included in the RESCUE study, vision was lost for an average of 4 months and the average best-corrected visual acuity (BCVA) just before treatment was 1.29 logMAR. During the first 48 weeks, vision continued to decrease in both eyes of each patient to reach a nadir. The primary end point was not met.

“Interestingly and unexpectedly, vision started to improve bilaterally from week 48 to week 96 in both the GS010- treated and sham-treated eyes,” Dr. Yu-Wai-Man said. “In fact, at week 48, vision had already begun recovering from the nadir.” By week 96, vision in the GS010-treated eyes improved by a mean of 26.3 letters from the nadir while in the sham eyes, vision improved by 22.8 letters.

A responder analysis was conducted, defined as an improvement of 10 or more letters if the patient’s BCVA was on-chart at its lowest point, or the ability to read a minimum of five letters or more if the VA was off-chart at its lowest point. Based on this definition, the responder rate was 63.2% in the RESCUE study. To put this into perspective, the responder rate was 27.9% in a retrospective natural history study.

In the REVERSE study, the same unexpected bilateral improvement in BCVA was observed in the GS010-treated and sham-treated eyes was also observed as in the RESCUE study. Using the same responder analysis that had been conducted for the RESCUE study, 67.6% of patients recruited into the REVERSE study achieved a clinically relevant visual recovery in BCVA.

Researchers performed a quantitative polymerase chain reaction assay at three months to detect and quantify the viral vector DNA in various parts of the eye, including the optic nerve, retina, optic chiasm, optic tract, and the lateral geniculate nucleus, but not in the visual cortex.

There was, therefore, evidence pointing towards the transfer of the viral vector from the injected to the contralateral uninjected eyes. This observation needs to be confirmed and it remains to be determined whether there is a diffusion pathway via the optic chiasm. The possible transfer of the viral vector between eyes provides a plausible explanation for the unexpected bilateral improvement seen in both the RESCUE and REVERSE studies.

According to Dr. Yu-Wai-Man, the data from the GenSight trials showed a continuous bilateral improvement in BCVA from week 48 to week 96.

“This improvement in BCVA was significant: GS010- treated eyes had a 26-letter average increase compared with the nadir in RESCUE and a 28-letter increase in REVERSE,” he concluded. “More than two-thirds of the combined number of participants in the RESCUE and REVERSE studies experienced a clinically relevant recovery from the lowest level of BCVA compared with 28% of patients in a retrospective natural history study.”

**NON-HUMAN PRIMATE STUDY**

To help determine the basis for the unexpected bilateral response, a study with non-human primates was undertaken to evaluate the biodistribution of the GS010 gene therapy vector. A unilateral injection of GS010 was administered in Cynomolgus monkeys. A quantitative polymerase chain reaction (qPCR) assay was performed at three months to detect and quantify the viral vector DNA in various parts of the eye and brain.

Three animals were treated with an injection of GS010 in the right eye and one control animal received a placebo intravitreal injection in the right eye. The treated animals, viral vector DNA was detected in all ocular tissues, but not in the tears of the injected eyes. In the fellow uninjected eyes, vector DNA was found in the anterior segment, optic nerve, retina, optic chiasm, optic tract, and the lateral geniculate nucleus, but not in the visual cortex.

This report was designated Best Paper in Session at the American Academy of Ophthalmology 2019 annual meeting. Dr. Yu-Wai-Man is an consultant to GenSight Biologics.
The third annual Ophthalmology Times® Research Scholar Honoree Program featured a wide range of research topics, from a quantitative analysis of lamellar macular holes to the incidence and features of uveal melanoma to the 20-year incidence of macular telangiectasia type 2.

Chair Rishi P. Singh, MD, Cole Eye Institute, said while the program “has built upon itself” year after year, he’s been particularly impressed with the science and quality of abstracts submitted this year, especially those that incorporated big data.

“Whereas we used to see studies with 40 or 50 patients, we’re now seeing them with 50,000 or 100,000 from a series of registries or other collections of groups of patients over time,” Dr. Singh said.

The judges also noted they are starting to see the distinction of being a Research Scholar Finalist listed on incoming résumés. Dr. Singh and fellow judges Thomas A. Albini, MD, Bascom Palmer Eye Institute; Sophie J. Bakri, MD, Mayo Clinic; Andrew A. Moshfeghi, MD, MBA, Roski Eye Institute; and keynote speaker Philip J. Rosenfeld, MD, PhD, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, had pre-selected 15 presenters from among more than 90 entrants. Each presenter was allowed 7 minutes to discuss their research, including what role they played in the research; the remaining 3 minutes were left for questions and answers with the judges.

“Congratulations on your research endeavor and thank you for trying to make a contribution to our field,” Dr. Singh said. “You put forward effort and passion to find insights into disease mechanisms and better treatments for our patients.”

This year’s winner, Shravani Mikkilineni, MD, MBA, resident, Henry Ford Hospital, presented on T2 Magnetic Resonance Assay for Detection of Ocular Candidiasis.

“The Infectious Disease Society of America guidelines still recommend that candidemia patients have a dilated fundus exam within one week of identification,” she said.

Dr. Mikkilineni noted that fungal blood cultures are currently the gold standard for diagnosing candidemia, but they can take 1-8 days for positive culture growth of Candida species, and false negatives can be as high as 50%, especially in the setting of antifungal use.
rioretinitis as compared to 47% for sensitivities of our T2MR test was 83%. Our most notable finding was that the were T2MR positive for Candida. So culture positive for endophthalmitis. Of these patients, 30 patients had chorioretinitis and three had definite ocular infections. Candida and 185 in a Growing Population.

The remaining top five finalists (in alphabetical order): Michael P. Ellis, MD, resident, UC Davis Medical Center, Cost Analysis of Tele-ophthalmology Screening for Diabetic Retinopathy Using Tele-health Billing Codes; Brad Jacobsen, MD, resident, Moran Eye Center, University of Utah, Salt Lake City, Prevalence of Retinal Diseases and Associated Risk Factors in an African Population from Mwanza, Tanzania.

Dr. Mikkilineni also explained that the T2 Magnetic Resonance assay (T2MR) is a newer nano-diagnostic FDA-approved approach to detect amplified DNA of Candida species from whole blood specimens, with a reported sensitivity of 89-98%, she said. Dr. Mikkilineni’s research evaluated whether the T2MR was superior to traditional blood cultures in detecting the ocular complications of candidemia, namely infectious chorioretinitis and endophthalmitis.

Of the 277 patients included in the study, 275 had blood culture testing and 245 had T2MR testing. Thirty-three patients (12%) had definite ocular Candida infections.

Of these patients, 30 patients had chorioretinitis and three had endophthalmitis. Of the patients, 178 were blood-culture positive for Candida and 185 were T2MR positive for Candida. So our most notable finding was that the sensitivity of our T2MR test was 83% for those patients with definite chorioretinitis as compared to 47% for blood cultures (P=0.016), she said. As the device is not at every hospital, it’s unclear what kind of clinical impact it may have for patients and those ordering the tests, she said.

“In most cases, a negative result is now confirmed 4-5 days after collection,” she said.

**A NEW APPROACH**

Dr. Mikkilineni also explained that the T2 Magnetic Resonance assay (T2MR) is a newer nano-diagnostic FDA-approved approach to detect amplified DNA of Candida species from whole blood specimens, with a reported sensitivity of 89-98%, she said. Dr. Mikkilineni’s research evaluated whether the T2MR was superior to traditional blood cultures in detecting the ocular complications of candidemia, namely infectious chorioretinitis and endophthalmitis.

Of the 277 patients included in the study, 275 had blood culture testing and 245 had T2MR testing. Thirty-three patients (12%) had definite ocular Candida infections.

Of these patients, 30 patients had chorioretinitis and three had endophthalmitis. Of the patients, 178 were blood-culture positive for Candida and 185 were T2MR positive for Candida. So our most notable finding was that the sensitivity of our T2MR test was 83% for those patients with definite chorioretinitis as compared to 47% for blood cultures (P=0.016), she said. As the device is not at every hospital, it’s unclear what kind of clinical impact it may have for patients and those ordering the tests, she said.

The remaining top five finalists (in alphabetical order): Michael P. Ellis, MD, resident, UC Davis Medical Center, Cost Analysis of Tele-ophthalmology Screening for Diabetic Retinopathy Using Tele-health Billing Codes; Brad Jacobsen, MD, resident, Moran Eye Center, University of Utah, Salt Lake City, Prevalence of Retinal Diseases and Associated Risk Factors in an African Population from Mwanza, Tanzania; Diana M. Laura, MD, resident, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Genotypic and Phenotypic Antibiotic Resistance in Staphylococcus Epidermidis Endophthalmitis; and Joseph Simonett, MD, resident, Casey Eye Institute, Blood Brain Barrier Disruption Maculopathy: A Common, Visually Significant Side-effect in a Growing Population.

**BECOMING A CLINICAL RESEARCHER**

Keynote presenter Dr. Rosenfeld advised attendees to choose research that targets an unmet need. “Even better, match your research with your scientific interests,” he said, “but bear in mind your interests must evolve.”

Success will depend on a researcher’s ability to recruit for clinical trials, Dr. Rosenfeld said. “There is no such thing as a quick and easy project,” he said. “Never forget your control arm.”

While retrospective subgroup analyses from prospective studies are necessary, “they should never be believed,” he said. “They’re useful for generating hypotheses, or confirming prior practices, but they need to be validated in prospective studies.”

If a phase 2 study is successful, “never change the protocol before the phase 3, and if the phase 2 study is unsuccessful, never design a phase 3 based on retrospective subgroup analysis,” he said.

As researchers become greater experts in a particular area, “people will seek you out to get your opinion. You’ll be exposed to novel ideas, treatments, and research projects,” Dr. Rosenfeld said.

Finally, he advised newer researchers to “Embrace the challenge of clinical research by asking the important questions. Go where the clinical need is greatest.” And, quoting Galaxy Quest, “Never give up—never surrender!”

**ABOUT THE RESEARCH SCHOLAR PROGRAM**

Ophthalmology Times® requested ophthalmic institutions to nominate fellows and residents involved in unique and notable research related to some aspect of retinal disease. Those who qualified were asked to submit an abstract and a 100-word summary of their work, plus prepare a presentation to include what the research contributes to the retinal community.

Supported by an unrestricted grant from Regeneron Pharmaceuticals, the top 5 finalists will be featured in a supplement to a peer-reviewed journal, and each received the Crystal Award.

All the presenters will have their research highlighted throughout the year in Ophthalmology Times® and online at OphthalmologyTimes.com. “These research programs are really foundational to making the next big step in our field to improve our patients’ lives and improve the lives of our caregivers,” Dr. Singh concluded.
Simultaneous Vision (SimVisGekko, 2EyesVision) is a visual simulator that provides patients with the experience of vision with multifocal intraocular lenses (mIOLs) before actual implantation, helping to manage patients’ expectations.

This innovation arose out of the scaling down of technologies that originated in astronomy, such as adaptive optics, into a system useful to ophthalmologists for prescribing correction for presbyopia and simulating multifocal lenses, according to Susana Marcos, PhD.

Despite the availability of mIOLs, she pointed out, only 7% of patients opt for this correction modality after cataract surgery.

‘This technology provides a powerful back-end.’

Prof. Marcos, a research professor at the Instituto de Optica Daza de Valdés, Consejo Superior de Investigaciones Científicas, Madrid, said she believes that the key may be the difficulty explaining multifocality to patients. In addition, it is difficult for patients to make a decision about mIOL implantation if they cannot visualize what their vision will be preoperatively, a scenario that leaves them with a great deal of uncertainty about both their expectations and the actual surgical results.

A solution to this may be use of the mobile SimVisGekko that would ease their decision-making process.

‘Visual simulators will help to sell more premium lenses and screen out prospective unhappy patients,’ Prof. Marcos explained. ‘This technology would be valuable for patients, clinicians, and IOL manufacturers.’

The device provides practical utility in the clinic, in that it improves patient satisfaction, facilitates comparison of corrective solutions, and saves time by providing an easy explanation of multifocality. It also provides business advantages by decreasing patient complaints and refunds, provides a competitive advantage to doctors who adopt the device early, and increases the number of mIOL prescriptions.

SimVisGekko is wearable, binocular, see-through, provides a 20-degree field of view, is programmable on a tablet and simulates multifocal and extended-depth-of-focus corrections and provides monovision or modified monovision correction.

‘This facilitates testing a range of preoperative corrections,’ she pointed out.

**HOW THE TECHNOLOGY WORKS**

The device contains an optotunable lens. Using a custom high-speed electronic driver, the lenses can change focus rapidly by a process called temporal multiplexing.

‘With periodic variations of the optical power at high speed, above 50 Hertz, static appearance of multifocal retinal images are provided by mapping spatial distribution in a lens into temporal distribution in the optotunable lens,’ Prof. Marcos described.

Dr. Marcos demonstrated this in a trifocal FineVision IOL. The map in the IOL is defined with a set of coefficients; the data show how much time the lens spends at the different power additions. With a trifocal lens the coefficients are at three different foci. This process can be performed with different coefficients and simulate extended-depth-of-focus lens types and different energy distributions.

‘We also control for dynamic effects in the lens so that we can really map the true focus performance of the lens,’ she said. A comparison of the performance of an actual commercial IOL with the simulation showed how well the images of the two matched.

**PRACTICAL APPLICATION**

When the SimVisGekko was taken into the clinic, it performed well. Prof. Marcos said researchers have found that the device replicates mIOLs.

‘We performed the test with a trifocal IOL in the SimVis preoperatively and the patient was ultimately implanted with the lens,’ she said. ‘We found that in patients with clear lenses and those with cataracts, the pre-operative (with SimVis) and post-operative (with the implanted IOL) defocus curved matched. In the presence of a cataract, there is a shift down because of the light distribution caused by the cataract, but the shape of the defocus focus curve is well captured.’

**MULTIPLE USES**

This technology is also useful for patients opting for multifocal contact lenses. An excellence replication of the contact lens performance on eye was achieved with the SimVis simulation. For different lens designs with different power additions.

The device also was tested using different natural images at far and near distances under conditions during the day and at night. When tested in a patient with, for example, corrected binocular far vision, the scores at the far distance were high and the scores for near were low. When bilateral bifocal correction was provided the far vision decreased slightly and the near vision improved. This also can be applied to monovision and modified monovision.

Prof. Marcos noted that when the patient is tested with different corrective options, surgery can proceed with much more certainty regarding the postoperative vision.

The physician can choose the desired lenses and control the test on an iPad. The management of the mobile device allows connection of every iPad to the cloud, remote management of the devices, security management, remote app updates, monitoring and tracking, and remote troubleshooting.

In addition, when new IOL designs become available the software is updated.

‘This technology provides a powerful back-end,’ she explained. ‘Over and above monitoring...’

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**TAKE-HOME**

- A visual simulator can provide patients with the experience of vision with multifocal intraocular lenses before actual implantation, helping to manage patient’s expectations.

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**CONTINUES ON PAGE 21:**

Presbyopia
Changing focus of accommodating IOLs now reaching a new level
Optic position changes to shift power from distance to near and back

By Lynda Charters; Reviewed by Stephen D. McLeod, MD

CHANGE IS A constant and with change in accommodating IOLs comes potential improvements in vision for presbyopic patients.

True accommodation means that the optic must instantaneously change power from distance to near and back. The most familiar strategy to accomplish this is a change in optic position, but other strategies to produce accommodation are changes in the lens curvature and in the refractive index or optic power, according to Stephen D. McLeod, MD, professor and chairman of ophthalmology, University of California San Francisco.

Regarding the lens position, surgeons are familiar with both the CrystaLens (Bausch + Lomb) and the Kellan Tetraflex (Lenstec). The Tek-Clear Accommodative Lens (Tekia), a lens with a 360-degree haptic structure and a single optic vault, is a slightly newer IOL than the previous two.

Lenses that depend on movement to change accommodation are limited in their ability to do so.

Dr. McLeod pointed out that an issue with all of these devices is limited by the typical optic powers required by patients who are emmetropic or low and high myopes.

“When dealing with an optic that moves forward, the degree of that movement is not great, often much less than 1 mm, and for most lens powers implanted, the observed degree of movement produces minimal accommodative change proportional to the power of the lens that is moving forward,” he said.

According to Dr. McLeod, the accommodative IOL models that change lens curvature can more efficiently effect the desired focus shift.

“For just about any IOL regardless of power, the amount of accommodative change that you get from the entire lens moving forward a given distance is an order of magnitude less than the accommodative change you get from an increase in curvature that shallows the anterior chamber by the equivalent amount,” he said.

The FluidVision IOL (PowerVision, now Alcon), a lens curvature IOL, is one of the older designs with peripheral reservoirs and distensible central optics. When the fluid moves from the reservoir to the center, the curvature changes.

The Opira accommodating IOL (Forsight Labs) is a sulcus-based device for which the haptics are fixed in the capsulorhexis. “The anterior optic accepts the fluid from the reservoir leading to the change in curvature,” Dr. McLeod said.

The Juvene IOL (LenGen) is based on the same principle as the Opira IOL. “This lens has two compartments. The anterior optic is the one that accepts the fluid from the reservoir, and the posterior element remains available for refining the focus power of the eye or for a toric correction,” he pointed out.

Atia Vision has also introduced in 2019 a modular presbyopia correcting IOL with the same basic approach that is comprised of a two-element design. The exception with this IOL is that the posterior element is the accommodative element. “The advantage that this lens offers is that if an adjustment of this optic is needed, it is far more accessible,” he said.

The Lumina IOL (AikoLens) is an example of the IOLs that use the third option for accommodating IOLs, i.e., change in the refractive index or lens power. This lens is comprised of two elements separated by an interface, a variable curvature cubic optic. “The anterior and posterior surfaces are displaced relative to each other and this setup changes the power of the intervening space,” Dr. McLeod pointed out.

Dr. McLeod also noted that the advantage of this design is the ability to achieve a "substantial change in the focal length with minimal ciliary body effect."

Because all of these approaches are mechanical, it raises the question about whether microfluidics or microelectronics can be put to better used to develop accommodating IOLs.

The Sapphire AutoFocus IOL (Elenza) may be one answer to that question. This lens changes focus power without moving and relies on a power cell and a chip embedded in the eye. The device has a remote recharging system in goggles that are worn while the patient sleeps.

“This is a paradigm-shift lens,” Dr. McLeod said, adding that the sensor for the device can detect change in the pupillary diameter, which triggers the electronics to send a signal to introduce a diffractive pattern on the optics.

The downsides are the large size, heavy weight and complex electronics, but as Dr. McLeod pointed out, it is showing us the direction in which accommodating IOLs are moving.

“There are many technologies under development in the accommodate arena,” Dr. McLeod concluded. “We are hopefully getting to the point at which we can actively change the true focus power of the system with truly accommodative devices in the reasonably near future.”

Prof. Marcos explained that the information is useful and is enabled by the fact that the preoperative clinical testing can be performed before surgery.

CONCLUSION
“We believe that SimVis represents a new paradigm in presbyopia correction that provides patient education, aid in lens selection, reduced uncertainty preoperatively, virtual clinical trials, the ability to test multiple lenses, and large data sets of patient preferences and usage,” she concluded.

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Prof. Marcos is a co-founder of SimVis Technology and co-founder and shareholder in 2EyesVision.

PRESBYOPIA

(Continued from page 20)

ing the use of the SimVis, we can monitor different patient lens preferences, the rates of actual implantations of those IOLs, and the conversion rate to multifocality.”
Pulsing or probing for MGD: How current devices compare

Current data offers physicians no clear conclusion about any particular technology

By Lynda Charters; Reviewed by Joanne F. Shen, MD

A FEW TECHNOLOGIES are currently available to facilitate pulsing or probing of the meibomian glands in dry eye disease. While each has advantages and disadvantages, current data are lacking to arrive at definitive conclusions about any particular technology, according to Joanne Shen, MD.

Dr. Shen is assistant professor of ophthalmology, Mayo Clinic College of Medicine, Scottsdale, AZ. Vectored thermal pulsation (VTP) (Lipiflow, Johnson and Johnson), which begins with instillation of a topical anesthetic, then possible manual exfoliation of the eyelid margins, and followed by automated expression of the glands with actuators; there are no steps required after the procedure.

Intense pulsed light (IPL) devices (Quadra Q4 Platinum Series, Dermamed; and M22, Lumenis) are FDA labeled for treatment of rosacea. Treatment for dry eye in the setting of rosacea begins with instillation of a topical anesthetic and shielding of the eyes from exposure to IPL.

Two passes of IPL placement are performed from tragus to tragus over the cheeks. With M22, the upper lids can be treated with a smaller handpiece. This is followed by manual expression using cotton-tipped swabs or specialized forceps. After the procedure, a nonsteroidal anti-inflammatory drug or a steroid may be used for two days.

Intraductal probing (IDP) (MGI probes, Katena) requires instillation of compounded topical 8% lidocaine in jojoba oil. The first step of the procedure is use of 1- to 6-millimeter blunt tip probes for intraductal placement followed by manual expression and possibly an intraductal steroid injection. After the treatment, topical steroids are administered, Dr. Shen said.

The obvious question is which method is better for treating obstructive meibomian gland disease.

VTP EVALUATIONS

A literature search disclosed seven studies of VTP, including five prospective randomized controlled studies and two prospective controlled studies. They were carried out nationally and internationally. In the groups that randomized VTP against other lid-warming techniques, such as hot and warm compresses, and other devices, one compared VTP with doxycycline twice daily. Dr. Shen pointed out that the average follow-up of the studies was one to 12 months.

“In the Lipiflow groups, symptoms improved and the meibomian glands yielded liquid secretions,” she said. “However, the atrophy of the glands seen on meibography did not change.”

IPL STUDIES

IPL was evaluated in one prospective randomized controlled study and five prospective controlled studies, all international trials. Three studies evaluated IPL only without expression versus controls, and the rest looked at IPL with meibomian gland expression versus expression only.

According to Dr. Shen, all of the studies reported that the symptoms and the tear break-up times improved. “One recent study found that the tear inflammatory markers decreased,” she said. “Another study found that the meibomian gland structure improved as seen by confocal microscopy, but there was no such improvement in the overall meibomian gland atrophy.”

Dr. Shen also noted that there was no consistent improvement in the Demodex mites with IPL.

Another IPL study from late 2019 reported on another indication for IPL plus MGX for moderate to severe blepharokeratoconjunctivitis (BKC). The 32 patients had been pretreated with steroids and antibiotics. One month later, 21 patients opted to undergo M22 IPL plus MGX sessions and 11 patients chose MGX only (controls). The investigators reported no recurrences of BKC in the treated group, while two of the controls (18.2%) had a recurrence during the four-month study.

The ocular surface disease index improved in both groups. The meibomian gland expression and meibum quality improved in the treatment group over the control group; however, the treatment group had significantly less meibomian gland atrophy, Dr. Shen pointed out.

TAKE-HOME

◗ There are a few technologies available today for the treatment of the meibomian glands in dry eye disease.

◗ Long-term data on probing and pulsing devices are needed to determine superiority.

CONCLUSION

Dr. Shen concluded that IDP controlled studies showed no endpoint treatment advantage versus conventional treatment at three months in two trials.

“No comparison studies were identified,” she said. “I would like to see VTP compared with IPL or MGX, IPL compared with IDP, and IDP compared with expression alone. There are no current data to determine which technology is most effective or safest, and long-term data are needed including monitoring of meibomian gland atrophy.”

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

FEBRUARY 1, 2020 :: Ophthalmology Times

BY LYNDA CHARTERS
There are many challenges to achieving success with advanced implants aiming to bioengineer the macula, according to Mark S. Humayun, MD, PhD. Dr. Humayun also offered a brief update on two projects that he has been leading to restore vision in patients with retinal degenerative disease – implantation of a bioelectronic epiretinal visual prosthesis (Argus II Retinal Prosthesis System, Second Sight Medical Products) for end-stage retinitis pigmentosa and subretinal implantation of a bioengineered retinal pigment epithelial (RPE) monolayer (California Project to Cure Blindness-Retinal Pigment Epithelium 1 [CPCB-RPE1], Regenerative Patch Technologies) for advanced dry age-related macular degeneration (AMD).

“Both bioelectronic and nanoscale scaffold approaches require a safe and effective abiotic-biotic interface with the ocular tissue,” said Dr. Humayun, Cornelius Pings Chair in Biomedical Sciences and professor of ophthalmology and biomedical engineering, director of the USC Ginsburg Institute for Biomedical Therapeutic and co-director of the USC Roski Eye Institute, Los Angeles. “As we look to leverage improvements in energy sources, materials, 3-D printing, and nanoscale fabrication along with growing interest of larger, traditionally nonmedical corporate partners bodes well for future development of these technologies.”

Visual Prosthesis

The epiretinal visual prosthesis has been implanted in 35 centers around the world in almost 400 eyes. It is FDA approved for implantation in the United States in patients who have light perception vision OU secondary to retinitis pigmentosa. In the European Union, the device is approved for use in patients with hand motion vision OU from retinal degeneration.

The device consists of extraocular components (a video camera attached to glasses and a video processing unit) and an intraocular implant consisting of an implanted microchip as well as an electrode array that is placed epiretinally.

“Both bioelectronic and nanoscale scaffold approaches require a safe and effective abiotic-biotic interface with the ocular tissue.”

Mark S. Humayun, MD, PhD

A patient uses the Argus II Retinal Prosthesis System to participate in archery as an instructor looks on. (Photo courtesy of USC)
**Rho kinase inhibitors: Filling a gap in glaucoma treatment**

Options include mechanism of action on trabecular meshwork without side effects

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

**IT IS SAFE** to say that the glaucoma medication market is thriving with therapies that can help the vast majority of patients achieve their target IOPs. The good news is that the products that comprise all of the various glaucoma drug classes are so highly efficacious as solo or combination therapies prescribed alone or in conjunction with additional drugs, that the need for glaucoma surgeries has decreased.

Two recently introduced anti-glaucoma drugs are adding to this success as a result of a new mechanism of action, high efficacy, a low treatment burden.

**NEW KIDS ON THE BLOCK**

Aerie Pharmaceuticals has developed two new drugs that have become commercially available recently. One is netarsudil ophthalmic solution 0.02% (Rhopressa), a rho kinase inhibitor, and the second is netarsudil and latanoprost ophthalmic solution 0.02%/0.005% (Rocklatan), a combination of a prostaglandin and a rho kinase inhibitor, according to Fiaz Zaman, MD, FACS, who is on the clinical faculty, University of Houston, and in private practice at Houston Eye Associates, Houston.

The FDA approval of netarsudil marked the first member of a new class of anti-glaucoma drugs to appear since 1996 when latanoprost ophthalmic solution 0.005% (Xalatan, Pfizer), a prostaglandin, entered the marketplace.

The beauty of this new drug class of rho kinase inhibitors is its unique mechanism of action to treat glaucoma, according to Dr. Zaman.

Previous classes of glaucoma drugs work to lower IOP by impacting the aqueous humor outflow or production; in contrast, rho kinase inhibitors work directly in the angle of the eye on the trabecular meshwork, with 70% to 80% of aqueous drainage occurring there, and the rest in the alternative pathway, the uveo-scleral pathway.

“[Netarsudil ophthalmic solution] targets the part of the eye that does most of the heavy lifting regarding aqueous drainage,” he said.

Other plusses of netarsudil ophthalmic solution are the absence of systemic side effects, making it useful for any patient with any medical condition eliminates, and a low treatment burden of one drop once daily, which contributes to increased patient compliance, Dr. Zaman explained.

“Many patients with glaucoma have IOPs that are in the normal to slightly elevated normal range,” he said. “Another benefit is that studies have shown that the efficacy of [netarsudil ophthalmic solution] is the same in patients with lower pressures as those with moderately elevated pressures. This is important, because with the other classes of glaucoma drugs, in patients with lower IOPs the efficacy is not as robust as in patients with moderate IOPs. [Netarsudil ophthalmic solution] works the same with these patients.”

Dr. Zaman uses netarsudil ophthalmic solution primarily in already treated patients who may need an additional medication to achieve the target IOP, in his practice that is about 70% to 75% of patients; the other 25% are using netarsudil alone. Any patient in whom the trabecular meshwork is visible is a candidate for this drug, such as in open-angle glaucoma, but not angle-closure glaucoma, he explained.

The other newbie, netarsudil and latanoprost ophthalmic (Rocklatan) received FDA approval in 2019.

In 1996, when latanoprost was the first prostaglandin to be introduced, it was initially a tertiary drop, i.e., a last resort of sorts for physicians because of uncertainty about its effects.

However, latanoprost was a game changer and the prostaglandins are now what Dr. Zaman describes as the “foundational drug” for glaucoma, with most patients starting on a prostaglandin; these drugs are dosed once daily and are highly efficacious with a safe systemic profile; the prostaglandin class has the highest efficacy data of all glaucoma drugs on the market.

**REDUCING IOP**

Latanoprost reduces IOP by its action on the uveo-scleral pathway; with netarsudil added, the two drugs promote aqueous outflow in the most comprehensive way possible by targeting both outflow pathways. This approach appears to be more beneficial to the overall health of the eye compared with all over anti-glaucoma drugs that decrease aqueous production.

“The aqueous has a purpose in the eye, i.e., it carries nutrients to the eye, to the lens specifically, and removes waste products from the eye,” Dr. Zaman explained. “Alteration of aqueous production has been hypothesized to induce earlier cataract formation.”

In contrast, Dr. Zaman noted that aqueous outflow drugs do not alter aqueous production, just augment outflow.

Dr. Zaman said he uses netarsudil and latanoprost ophthalmic with patients with an open-angle glaucoma and as a substitute for patients already on a prostaglandin who are not adequately controlled. Treatment-naive patients also can benefit to achieve aggressive control from the outset of therapy.

A downside to these two new rho kinase inhibitors that is attributable to netarsudil is the potential development of conjunctival hyperemia, which in about 10% of patients can be moderate to severe and in about 30% to 50% mild and transient.

**GLAUCOMA MEDICATION MARKET OVERVIEW**

The prostaglandins currently have the highest share of the glaucoma market for all of the reasons listed previously, i.e., once daily dosing, high efficacy, safe systemic profile, and it is well tolerated by patients. The prostaglandins tick all of these boxes.

Hyperemia also can be a side effect of the prostaglandins, as can lash growth and slight skin discoloration under the eyelid. Rare side effects include changes in iris color and swelling of the retina.

Among prostaglandins that are available are bimatoprost (Lumigan, Allergan); travoprost (Travatan Z, Novartis); tafluprost (Zioptan, Akorn), and latanoprostene bunod (Vyzulta, Bausch + Lomb).

In addition to the rho kinase inhibitors and prostaglandins, the other classes of glaucoma drugs with a share of the market are the beta-blockers, alpha-agonists, and carbonic anhydrase inhibitors (CAIs).

These drugs are prescribed as single therapies as well as in combination with a drug from another class.

Continues on page 26: Glaucoma
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**BIOELECTRONICS**  
(Continued from page 23)

this goal,” Dr. Humayun explained. The approach is designed to ultimately allow blind people to be able to read and recognize faces. In its current version, it mainly serves to improve patients’ orientation and mobility. By doing so, the epiretinal prosthesis still provides significant benefits because it permits re-engagement in activities of daily living therefore increases well-being.

“Patients implanted with the prosthesis report that it has allowed them to walk safely within a crosswalk, locate doors and windows, detect and track other people, and sort light and dark clothes,” Dr. Humayun said. “With the prosthesis they feel more socially connected and some patients have been able to participate in recreational activities such as bowling, archery, and even skiing.”

Initially, the best visual acuity achieved with the implant was 20/1,200. However, thanks to software enhancements and better surgical placement, function has improved to 20/480, and it can reach 20/200 with digital zoom. Dr. Humayun reported that the team is now working to provide color vision that will help patients with object recognition at lower resolutions.

**RPE TRANSPLANTATION**

Multiple approaches are being investigated for RPE transplantation to restore vision in patients with advanced dry AMD.

**GLAUCOMA**  
(Continued from page 24)

The primary mechanism of action of these drugs is to decrease aqueous production.

The beta-blockers that are used by ophthalmologists include timolol maleate 0.5%; timolol maleate ophthalmic gel forming solution 0.25%, 0.5%; timolol maleate; timolol hemihydrate 0.25%, 0.5%; betaxolol HCI 0.25%, 0.5%. metipranolol 0.3%; and levobunolol HCl ophthalmic solution 0.25%, 0.5%.

The available CAIs are acetazolamide; brinzolamide ophthalmic suspension 1%; dorzolamide HCl 2%, and methazolamide.

**COMBINATION DRUGS**

A number of combination drugs are on the market that combine drugs for a more encompassing effect. Combigan (Allergan) is one such drug that combines an alpha-agonist (brimonidine) with a beta-blocker (timolol); dosing is twice daily and it is highly efficacious. Dr. Zaman uses it as an additive drug. In some patients this drug can cross the blood-brain barrier resulting in sleepiness.

Another combination drug is Cosopt (Merck & Co.), which is comprised of a beta-blocker (timolol) and a CAI (dorzolamide). This also is doses twice daily and lowers IOP well. Systemic side effects include, for example, low blood pressure and fatigue.

Simbrinza (Alcon) combines a CAI (brinzolamide) and alpha-agonist (brimonidine), combination medication consisting of (alpha-agonist). Without a beta-blocker, this drug is indicated for patients with asthma and is dosed three times daily. Shaking the bottle is mandatory because the active ingredient sinks to the bottom.

“The glaucoma medications have improved over time with increased efficacy,” Dr. Zaman concluded. “Patients are achieving lower pressures recently with a resultant fewer glaucoma surgeries.”

Fiaz Zaman, MD, FACS

“The glaucoma medications have improved over time with increased efficacy. Patients are achieving lower pressures recently with a resultant fewer glaucoma surgeries.”

Fiaz Zaman, MD, FACS

Dr. Zaman is a speaker for Aerie Pharmaceuticals and Allergan.

Dr. Humayun and colleagues are working with a polarized monolayer of human embryonic stem cell-derived RPE on a non-biodegradable, synthetic parylene scaffold.

“Injecting a cell suspension is technically easier,” he said. “Transplantation of RPE as a confluent sheet on a supportive scaffold, however, assures that the cells adhere with the proper orientation that is critical for survival and growth factor production by the RPE.”

According to Dr. Humayun, his research team has spent five years working on the development of an erodible substrate for the RPE sheet, but then turned to use of parylene, which is non-erodible polymer that combines an alpha-agonist (brimonidine) with a beta-blocker (timolol); dosing is twice daily and lowers IOP well. Systemic side effects include, for example, low blood pressure and fatigue.

Simbrinza (Alcon) combines a CAI (brinzolamide) and alpha-agonist (brimonidine), combination medication consisting of (alpha-agonist). Without a beta-blocker, this drug is indicated for patients with asthma and is dosed three times daily. Shaking the bottle is mandatory because the active ingredient sinks to the bottom.

“The glaucoma medications have improved over time with increased efficacy,” Dr. Zaman concluded. “Patients are achieving lower pressures recently with a resultant fewer glaucoma surgeries.”
Patients with severe cases of ocular surface disease can be some of the most challenging in ophthalmology, and cannot be treated with a “cookbook” approach. Often, these patients require a physician to pull out all of the stops in the treatment armamentarium.

The first step is keeping the inflammation under control. Without that control, the patient can slide down a path filled with hurdles to improving their ocular health. According to Clara C. Chan, MD, FRCSC, FACS, assistant professor of ophthalmology, University of Toronto, Department of Ophthalmology, and medical director, Eye Bank of Canada, Ontario Division, the importance of the conjunctiva cannot be overemphasized. “The tissue allows for monitoring of inflammation,” she said. “The goblet cells, which secrete the mucin layer of the tears, are a hallmark of healthy conjunctival tissue. When goblet cells are identified on the corneal surface it is diagnostic of limbal stem cell deficiency (LSCD).”

In addition to LSCD, other sequelae of conjunctival inflammation are goblet cell loss, mucin deficiency, symblephara formation, loss of the fornices, and end-stage surface keratinization, Dr. Chan pointed out. The salvage options are very difficult once patients have run the gantlet of these ocular insults.

Dr. Chan explained that eyes with chronic conjunctival inflammation and total LSCD have the worst prognosis with any surgical intervention. “The sequelae of LSCD are daunting, and include conjunctivalization, visual loss, chronic pain with persistent epithelial defects, photophobia, red eye, and corneal transplant failure,” she said.

Patients with more than 50% LSCD and active conjunctival inflammation such as those with Stevens-Johnson syndrome, mucous membrane pemphigoid (MMP), and recent chemical or thermal injury, can expect the worst outcomes.

Pearls for management of ocular cicatricial disease

Controlling inflammation key to successful treatment strategy for patients

By Lynda Charters; Reviewed by Clara C. Chan, MD, FRCSC, FACS

Ocular cicatricial disease requires a step-wise approach to secure the best results.

TAKE-HOME

Good history-taking is mandatory for identifying the some of the ocular offenders in plain sight that can be overlooked, such as topical formulations with preservatives and glaucoma medications that can damage the ocular surface with chronic use.

In addition, a medical history of atopy, graft-versus-host disease, and Stevens-Johnson syndrome can create cicatrical changes on the ocular surface. The physician should also be alert to a history of infections, i.e., herpes simplex virus, and adenovirus; trauma from chemical/thermal injury, or radiation; and inflammation from rosacea and chronically treated refractory blepharitis.

The presence of a disease such as MMP with ocular involvement is not

Continues on page 29: Management
Connect the dots: Diagnosing, managing multifocal choroiditides

Amid multiple prognoses, early treatment is key to success

By Lynda Charters

THE VARIOUS MULTIFOCAL choroidopathies differ in course, prognosis, and treatment. While the prognoses do differ, they are hopeful with early treatment in most cases.

Acute posterior multifocal placoid pigment epiretinaldysplasia (APMPDE) and multiple evanescent white dot syndrome (MEWDS) are self-limited, spontaneously remitting diseases for which treatment typically is not needed.

For both, the prognoses are reasonably good and excellent, according to Douglas Jabs, MD, MBA.

Roughly 75% of patients with APMPDE have a final visual acuity (VA) of 20/40; about 5% have a final VA of 20/200 or worse. Regarding treatment of APMPDE, administration of corticosteroids does not make a sizable difference in the visual outcomes compared with no treatment.

“There is little evidence regarding the benefit of corticosteroids for these patients,” noted Dr. Jabs, a professor of epidemiology, The Johns Hopkins University Bloomberg School of Public Health, and professor of ophthalmology, The Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore.

Likewise with MEWDS, the average VA outcome is very good, 20/21, and 95% of patients achieve 20/25 or better without treatment.

Patients with central nervous system or systemic vasculitis can have a scenario similar to APMPDE in the eye. The vasculitis should be treated with corticosteroids and immunosuppression.

Patients with birdshot chorioretinopathy (BSCR) lose vision as the result of macular edema and progressive visual field loss. Corticosteroids can effectively treat the macular edema but treatment with doses of 15 mg daily or less results in recurrence of the macular edema, and that dose is too high for safe use over the long term. A safe long-term dose is half of that dose (i.e. 7.5 mg/day or less).

Immunosuppressive therapy was reported to significantly (P = 0.009) prevent the recurrent macular edema by 83%. “This result suggested that treatment of BSCR should start with oral corticosteroids and immunosuppression,” Dr. Jabs said.

Importantly, studies also have shown that pre-treatment visual field damage is reversible to some degree. Indocyanine green angiography has shown resolution of the BSCR spots as well as resolution of the damage in the ellipsoid zone on optical coherence tomography images, he commented.

“These results suggested that patients with BSCR can benefit from early immunosuppression therapy along with corticosteroids from the outset of therapy,” he stated.

Multifocal choroiditis with panuveitis (MFCPU) is associated with a very poor visual prognosis if left untreated.

A series of cases from Johns Hopkins showed that about half the eyes presented with impaired vision, although fewer patients were blind bilaterally, Dr. Jabs reported. Administration of oral corticosteroids at doses less than 10 mg daily were ineffective, although at doses greater than 10 mg daily they were effective; this suggested that corticosteroid therapy alone was insufficient for these patients, as the disease could not be controlled with doses safe for long-term use.

The key factor for MFCPU seemed to be administration of early immunosuppression treatment, which in one study reduced the likelihood of structural complications with an 83% benefit and markedly reduced the likelihood of blindness by over 90%. This again is another disease in which treatment should be initiated with both immunosuppression and oral steroids, Dr. Jabs suggested.

Punctate inner choroidopathy (PIC) is characterized by a highly variable course and a good prognosis in response to combination therapy of anti-vascular endothelial therapy (VEGF) and immunosuppression. In some cases, it will respond to only anti-VEGF therapy.

Dr. Jabs described a case that presented before the use of anti-VEGF therapy for this pathology. The patient’s disease spontaneously went into remission.

The only complication was choroidal neovascularization (CNV), which also resolved spontaneously. The patient was not treated. Currently, he likely would have received anti-VEGF therapy for the CNV.

This patient may be the exception. Some patients may experience chronic bilateral CNV that can persist despite treatment with anti-VEGF therapy. Dr. Jabs noted that those patients may improve with immunosuppression therapy, and the likelihood of development of CNV will decrease if the inflammation becomes inactive.

CNV occurs quite often in patients with PIC. “It is the complication that drives therapy for patients with PIC,” he said.

Two case series of patients with PIC, one from the University of Illinois at Chicago and one from Johns Hopkins found that the VA was maintained at at least 20/40 in at least one eye, and the rates of blindness were low, although not zero. The results again suggested that with PIC early immunosuppression therapy preserves vision by preventing recurrent CNV, Dr. Jabs commented.

A study at the Icahn School of Medicine at Mount Sinai investigated treating, MFCPU, PIC, and BSCR, with immunosuppression therapy and found that the VA in patients with these diseases was maintained over a two-year period. In addition, the visual fields in the patients with BSCR could be increased. The investigators also lowered the corticosteroid doses to enable long-term dosing.

Dr. Jabs pointed out that in some cases, the dose of immunosuppression therapy required maximization. Two immunosuppressive drugs were needed in some cases.

The relatively few data that are available for this disease suggest that if left untreated it is progressive and ultimately affects both eyes with substantial visual loss. Immunosuppression therapy was shown in small series of patients to stop disease progression and relapses.

Alkylating agents effectively treat serpiginous choroiditis but they are associated with long-term side effects, including an increased risk of cancer, and therefore largely have been abandoned.

“Chronic immunosuppression appears to improve the prognosis for these patients,” Dr. Jabs said.

In adults requiring immunosuppression, Dr. Jabs begins with 1 mg/kg/day of prednisone or...
always evident initially and the condition of the ocular surface—the persistence of inflammation—can escape the control of the treating physicians. Determining the etiology of the inflammation clearly is important to keep it in check.

Dr. Chan noted that MMP can be misdiagnosed and managed as blepharitis for years (stage 1). With no improvement, a biopsy of the abnormal conjunctiva is performed (stage 2). Symblephara forms (stage 3) and end-stage keratinization (stage 4) develop with resultant poor prognosis. Patients need systemic immunosuppression to control the inflammation.

Patients often need a combination of long- and short-term treatments to optimize the ocular surface that include lubricants, anti-inflammatory drugs, nutritional support, management of lid margin disease, and adjunctive therapy such as punctal plugs, environmental changes, elimination of agents toxic to the ocular surface, changes in systemic medications, scleral contact lens, among others.

**STEPS TO SUCCESS**

**Step 1** In managing patients with cicatricial disease is optimization of glaucoma with early placement of a tube shunt and eliminating the toxicities from glaucoma medications.

**Step 2** Involves correcting lid abnormalities such as entropion, trichiasis, exposure, keratinized lid margins, and lagophthalmos. If left uncorrected, reconstructive efforts will have a poor prognosis, Dr. Chan commented.

**Step 3** Calls for suppressing ocular surface inflammation and autoimmune responses. This can be accomplished with topical instillation of treatments or systemic therapies. “This can take months or years to achieve,” she emphasized. Patients with chemical burns treated with inflammatory suppressive measures do much better sometimes up to a decade.

**Step 4** Is a preemptive trial of scleral contact lenses to avoid surgery. If the contact lens fails, ocular surface reconstruction is a consideration. “Scleral contact lenses,” she noted, “have revolutionized how I manage these patients. Often, this is the point at which we can stop and not need to go on with other interventions.”

Two commonly used scleral contact lenses used in Dr. Chan’s patients are the prosthetic replacement of the ocular surface ecosystem (PROSE, Boston Foundation for Sight) and the impression-molded EyePrintPro (EyePrint Prosthetics), a clear device that is custom fitted onto the eye surface.

Dr. Chan described the case of a 21-year-old patient with monocular vision who had Stevens-Johnson syndrome and was fitted with the EyePrintPro and achieved a best-corrected visual acuity of 20/30 in his functioning eye.

“We did not have to do stem cell transplantation, avoided systemic immunosuppressive therapy, and his vision has been maintained for 10 years,” she said.

**Step 5** Involves ocular surface stem cell transplantation in which either the limbal stem cells or the conjunctiva can be transplanted for patients for whom the previous steps failed. Symblepharon and ankyloblepharon lysis can be performed, and the fornix can be re-formed to facilitate wearing of therapeutic contact lenses. The Boston Keratopros thesis (Kpro Type 1) can be implanted if there are contraindications to systemic immunosuppression, Dr. Chan noted.

A number of types of stem cell transplants are available. Conjunctival limbal allograft or autograft are indicated for mild/moderate disease. Keratolimbal allografts use cadaver donors and are reserved for moderate and severe disease in the absence of suitable donor; these grafts serve as complete barriers to conjunctivalization and are secured with glue and sutures and reepithelialize from between 1 to 3 months postoperatively, according to Dr. Chan.

A combination approach, i.e., the Cincinnati Procedure, uses both live and cadaver tissue. “This provides greater replenishment of goblet cells as well as a 360-degree limbal stem cell barrier,” she explained.

**Step 6** Is the final step—optical corneal transplantation. The surgical choices are deep anterior lamellar keratoplasty, penetrating keratoplasty, Kpro type 1 if the previous two fail, or Kpro type 2 if Kpro type I fails. “The patient must have ongoing surveillance for glaucoma, infection, corneal melt, retinal detachment, sterile vitritis, endophthalmitis, or erosion,” Dr. Chan advised.

**PEARLS**

According to Dr. Chan, symblepharon formation may indicate that much more is going on as in the case of a patient referred for a biopsy to rule out MMP. The biopsy uncovered squamous cell carcinoma.

Symblepharon after epidemic keratoconjunctivitis also can be associated with binocular diplopia with side gaze. After dry eye and inflammation were addressed, the symblephara were freed and an amnion graft placed into the conjunctival defect and fornix.

The key to success is to allow conjunctival reepithelialization before symblephara re-forms.

Keratolimbal allograft segments can be used to treat symblephara that form as the result of mechanical and iatrogenic trauma, such as orbital floor fractures, tree branch injuries, and blepharoplasty gone awry.

Dr. Chan described an unusual case in which an unexpected cataract surgery was complicated by symblepharon formation to the wound, postoperatively. The patient reported eye pain, fatigue, severe weakness, abnormal complete blood count, and bone marrow biopsy that resulted in an ultimate diagnosis of leukemia which was the underlying cause for paraneoplastic pemphigus, which requires treatment of the malignancy and immunosuppressive therapy.

“A step-wise approach with a multi-disciplinary team is needed for ocular surface reconstruction in cicatricial diseases,” she concluded. “Therapeutic scleral contact lenses can delay or obviate the need for surgery.”

Biopsy acute symblepharon to rule out squamous cell carcinoma and MMP. MMP can be a paraneoplastic manifestation.

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This article is based on Dr. Chan’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Chan has received prior honoraria or research funds from Alcon, Allergan, Bausch + Lomb, Johnson & Johnson, Lathibian Thera, Santen, Shire, TearLab, and Zeiss.

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This article is based on Dr. Jabs’ presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Jabs has no financial interest in any aspect of this report. Most treatments referred to are administered on an off-label basis.
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**VERMONT**

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

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Interested individuals should apply online at https://www.uvmjobs.com/postings/32453 (position number 006035).

Inquiries may be directed to Dr. Brian Kim c/o Kristin Allard at Kristin.Allard@uvmhealth.org.
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The Division of Ophthalmology in the Department of Surgery at the Robert Larner, M.D. College of Medicine at the University of Vermont and its affiliated medical center, The University of Vermont Medical Center, is recruiting a full-time academic Comprehensive Ophthalmologist. This individual must have completed a board approved 3- or 4-year ophthalmology residency, be board certified or board eligible, and eligible for medical licensure in the State of Vermont. The candidate must have demonstrated interest and ability in teaching medical students and residents and be willing to participate in the surgical teaching programs. This academic appointment will be in the non-tenure clinical scholar pathway at the Assistant or Associate Professor level commensurate with experience and training.

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Interested individuals should apply online at https://www.uvmjobs.com/postings/37767 (position number 00022902). Inquiries may be directed to Dr. Brian Kim via Kristin Allard at Kristin.Allard@uvmhealth.org.
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Artwork by Jon Carter

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