ARTIFICIAL INTELLIGENCE (AI)-ENABLED radar may be an improvement over the traditional method of visual field analysis. Investigators note that by using AI-enabled radar they can better assess the functionality of patients with glaucoma and determine which patients have slowly and rapidly progressing visual field damage.

This technology is designed to address the shortcomings of traditional visual field analysis, specifically, that they rely on traditional paradigms such as linear regression and do not generate detailed results beyond progression or no progression, do not provide objective identification of progression, and lack advanced visualization and interpretation, according to Siamak Yousefi, PhD.

“We have proposed a glaucoma radar, a dashboard, that is a pipeline of information,” he explains. Continues on page 22: Radar

THERAPEUTICS

FOCUSING ON TREATMENT OF ORBITAL INFLAMMATORY DISEASE

By Cheryl Guttman Krader, BS, Pharm; Reviewed by Louise A. Mawn, MD

MEDICAL MANAGEMENT OF orbital inflammatory disease (OID) is based on the use of non-specific and specific immunomodulatory drugs. Patient care is optimized by determining underlying etiology for the inflammation, according to Louise A. Mawn, MD, professor of ophthalmology and neurological surgery, Vanderbilt University Medical Center, Nashville, TN.

“Orbital inflammation is a response of the immune system and not a diagnosis in itself,” she explained.

When faced with medical management, Dr. Mawn said physicians first have to know what it is they are treating and how to manage the unknown.

Continues on page 24: Inflammatory
VISION TO LIVE

SCIENCE IS JUST THE BEGINNING OF OUR INNOVATION.
LET’S PARTNER IN DOING MORE TO GIVE PEOPLE THE
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MARCH 15 MARKS the idea of March, the first day of the Roman New Year and a time to remain vigilant.

And vigilance is important amid the coronavirus issue. To that end, the Ophthalmology Times® team is working to be the voice of reliable coverage of the coronavirus, detailing the facts without any hype. For the latest ophthalmology-related information, you can follow us on social media. You also can find coverage online at OphthalmologyTimes.com/Coronavirus.

In this issue of Ophthalmology Times® we also look at technology that can change the ophthalmic landscape. Our lead cover article, in device technology, focuses on artificial intelligence-enabled radar, which some view as an improvement over traditional visual field analysis. Siamak Yousefi, PhD, discusses the technology, which is designed to address the shortcomings of traditional visual field analysis.

Therapeutics also is on this issue’s cover. Louise A. Mawn, MD, details the treatment of orbital inflammatory disease. Corticosteroids and a variety of other non-specific and specific immunomodulatory drugs are used in the medical management of orbital inflammatory disease. Establishing a diagnosis guides targeted patient care.

Our surgery core in this issue offers some interesting topics that can help you offer improved surgical outcomes for patients. William J. Dupps, MD, offers insight on improving LASIK outcomes with biomechanical analysis. He said he believes that 3D biomechanical measurements from Brillouin imaging or optical coherence elastography (OCE) could bring even more predictive power to simulations by better charactering individual properties and the effects of different procedures.

Also on the surgery front, Arthur B. Cummings, MD, discusses finding options with presbyopia-correcting IOLs, which can be used in “borderline” postkeratorefractive patients. Cataract surgeons are gaining confidence using presbyopia-correcting IOLs in patients with a history of keratorefractive surgery.

Imaging content in this issue focuses on technology devices and cloud technology, which is evolving with an eye on taking advantage of smartphone technology. Stephen D. Klyce, PhD, FARVO, tells us that topographers and tomographers available today have a growing number of capabilities, including pachymetry, wavefront aberrometry, pupillometry, air puff tonometry, auto-refraction, screening programs, IOL biometry, cataract grading, dry eye parameters, and contact lens fitting.

We continue our device technology coverage with a dive into modular curvature-changing fluid IOLs. Eric Donnenfeld, MD, notes that the potential presbyopia market is huge, and a new IOL that provides 3D of accommodation in additional mimicking the crystalline lens and filling the capsular bag offers good stability and little posterior capsular opacification.

Ophthalmologists and optometrists can work together when treating patients with dry eye disease. Cynthia Matossian, MD, FACS, details two scenarios in which dry eye disease presents an opportunity for ophthalmologists and optometrists to work together for the benefit of our patients.

Clinical diagnosis content examines fluorescein angiography, one of the oldest procedures used by ophthalmologists, but still a valuable tool. Steven Yeh, MD, discusses the patterns of various diseases and how FA adds to the clinical evaluation of these patients. Vishal Jhanji, MD, tells us how advances in hardware and software make corneal topography and tomography useful tools for ectasia risk screening and for the diagnosis and follow-up of keratoconus and post-LASIK ectasia, but other factors and clinical correlation are important when interpreting the findings.

Our gene therapy core coverage will examine the association of the genetic variations with keratoconus, and this issue also features a special section, Breakthroughs in Retina Therapeutics.
Can we hack aging?
Specific targeted action may help us turn back the clock

A FEW YEARS BACK, I read with interest an editorial by Peter J. McDonnell, MD, detailing a patient he treated who had survived the Bataan Death March in the Philippines.

During my residency training in ophthalmology at Tulane University, I spent time at the VA Hospitals in New Orleans and Biloxi and had the privilege of treating many veterans who had survived extremely harsh conditions similar to Louis Zamperini in the story “Unbroken.”

PLANE SHOT DOWN
Zamperini’s plane was shot down in the Pacific in May 1943 and he then spent 47 days drifting in the ocean in a small raft. He and one other survivor were immediately captured by the Japanese Navy when they approached the Marshall Islands. He went on to endure two years of intense suffering in Japanese POW camps. He was exposed to near starvation, constant cold, and extreme physical labor and torture—and yet, he survived. He later ran a leg of the Olympic Torch relay in Nagano Japan prior to the 1988 Winter Olympics and continued to bike around Los Angeles and attend USC football games into his 90s. He lived a long, healthy life until he died at the age of 97 in 2014.

How is that possible? Were these men who survived the Bataan Death March or years in a POW camp blessed with resilient uber-genes that their fellow soldiers did not possess or did the ordeal they survived somehow change them and lead to a longer and healthier life? How can someone who went through such an ordeal live longer and healthier than most of us who experience a sheltered, comfortable existence?

It turns out that new research may hold the answer.

In my hometown of Pensacola, FL, the Institute for Human and Machine Cognition produces a terrific podcast called STEM Talk in which a visiting scientist or researcher is interviewed regarding his or her area of expertise.

The podcast is typically an hour or two and reviews topics such as astronomy, climate, aviation, or artificial intelligence. However, my favorite topics are those covering diet, exercise, health, and aging. I am a former college basketball player and physician and thought that I was reasonably up-to-date in the areas of health and fitness until I began listening.

I have learned about intermittent fasting, efficient weight training, high-intensity interval training, caloric restriction, and the benefits of a ketogenic diet and hot and cold stress.

MODIFIED AGING
Many of the experts on STEM Talk argue that aging is not preordained and can be modified through specific targeted action.

Harvard professor David Sinclair, PhD, makes the point in his book, “Lifespan,” that physical stressors can alter our epigenetic makeup and may lead to a longer life span and health span. He and others believe that hormesis—“a level of biological damage or adversity that stimulates repair processes that provide cell survival and health benefits”—is largely responsible.

In other words, what does not kill you makes you stronger!

Dr. Sinclair also discusses compounds that might extend life, in essence, by simulating hormesis such as NAD boosters, metformin, resveratrol, and rapamycin.

Are the veterans that we have probably all seen in the VA Hospital system somehow the beneficiaries of hormesis after surviving near starvation, extreme physical demands and chronic cold stress?

In the end, it seems only fitting that men such as Zamperini who survived near death in a POW camp would have a few extra years of healthy living after what he went through.

Maybe we can hack our aging processes by harnessing hormesis and live longer and healthier lives by implementing some of these ideas.

By Tim B. McLaughlin, MD
Eye Institute at Medical Center Clinic
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READ THE ORIGINAL COLUMN
Visit our website to read the editorial by Peter J. McDonnell, MD, that inspired Tim B. McLaughlin, MD.

Read the editorial online: OphthalmologyTimes.com/Editorials/ResidentsMemory
Most technologies naturally evolve over time. However, in the case of LASIK, does the procedure need to? William J. Dupps Jr., MD, PhD, made his case for the impact of biomechanical information and how structural considerations may actually improve outcomes.

“Isn’t LASIK good enough?” asked Dr. Dupps, professor of ophthalmology, Cole Eye Institute, Cleveland Clinic. “Why do we need to worry about biomechanical or structural assessment? We are doing just fine.”

This is a common sentiment, noted Dr. Dupps, adding that he believes that most surgeons still are looking for ways to deliver even safer, more precise outcomes.

Dr. Dupps describes what he calls a “precision gap” in refractive surgery planning.

“There is a remarkable degree of precision available in our preoperative assessment tools on one hand and in the treatment delivery systems on the other,” he said. “But there is a striking gap in how we leverage those capabilities to develop and customize treatment plans.”

Moreover, Dr. Dupps noted that surgeons leave a lot of information on the table when they take a plan to the operating room.

“If we are seeking ultimately to reduce the number of refractive outliers, improve the ability to dial in very specific optical outcomes in individual cases, and minimize the risk of structural weakening that can lead to refractive outliers or progressive corneal instability, then we will need to develop treatment planning paradigms that incorporate preoperative corneal biomechanical information and use all pertinent outcome-driving data in our predictive models,” he said.

Current Status of Planning

Dr. Dupps pointed out that most refractive surgery treatment planning—whether for LASIK, PRK, SMILE, intracorneal rings, or incisional refractive surgery—is currently retrospective, i.e., based on historical outcomes; probabilistic and not deterministic; and minimally personalized in that treatment plans are often driven by a very limited subset of the patient’s data.

For example, most laser refractive surgery is performed using only the refractive error as an input, which some surgeons modify using nomogram software packages that generate empirical treatment adjustments based on previous outcomes for that treatment system. A smaller number of procedures are performed using customized topography or wavefront-guided treatment patterns, but even in these treatments, large amounts of potential outcome-driving features of the patient are not used in treatment planning.

“All corneal refractive procedures are either directly mediated by biomechanical effects (incisions, corneal ring segments and crosslinking) or affected by them (LASIK, PRK and SMILE), yet we lack a unifying clinical decision tool that uses this knowledge in a predictive way,” Dr. Dupps said.

Seeing Below the Surface

Specifically, Dr. Dupps said he believes that a comprehensive biomechanical assessment is crucial for better detecting the risk of ectasia and for advancing efforts to personalize refractive treatments. He points to two key components of structural assessment: biomechanical measurement and structural modeling.

Regarding modeling, he described a computational approach to prediction and risk assessment that is highly specific to individual eyes and patients. This technology originated in his research lab and has been further developed from commercialization through a Cleveland Clinic spinoff company, OptoQuest.

The software application, called SpeciEye, imports three-dimensional anatomy from a standard tomographer and other clinical data. A finite element model mesh of the whole eye is then built from that anatomy. Standard ocular material properties are incorporated but could be customized as measurement technologies become available for this.

The next step is verification. The eye model is loaded with the patient’s IOP and confirms that the resulting topography of the eye is similar to that of the patient. After this, the surgeon enters details of a proposed procedure, which the finite element model then simulates in the cloud on the virtual eye.

“This results in a predicted postoperative model complete with regional stresses and strains,” Dr. Dupps explained. “These data and ray-traced estimates of refractive change from the model surfaces are then translated into treatment guidance information to the clinician.”

Individual Differences

To determine if individual variations in corneal stiffness affect LASIK outcomes, Dr. Dupps and Abhijit Sinha Roy, PhD, performed a study using the same corneal geometry from an eye and ran multiple myopic LASIK simulations with a range of corneal stiffness values from the experimental.

In eye models with a stronger cornea, the limbus shifted outwardly while the central cornea displaced posteriorly, all as a result of simulated flap creation and ablation. In contrast, in a weaker cornea with low corneal stiffness, the procedure resulted in forward displacement of the corneal apex.

“There is a warpage phenomenon that occurs as the stresses and strains redistribute after flap creation and ablation, and these can produce clinically significant differences in refractive outcome,” Dr. Dupps said.

These results were reported in the *Journal of Refractive Surgery* (2009;25:875-887).

The structural shifts observed in a stiff cornea contribute to further flattening of the refractive outcome, possibly resulting in overcorrection. In the cornea with low stiffness, the forward protrusion decreases the myopic correction, resulting in relative undercorrection.

In the presence of an immediate undercorrection, a weaker cornea should be suspected and the patient followed before performing an enhancement. The results achieved with the eye model were validated in 19 actual LASIK cases and compared with simulated results. Dr. Dupps reported “a very high correlation between the actual and predicted outcomes (Invest Ophthalmol Vis Sci. 2017;53:444-453).”

The study also showed that including an adjustment for the preoperative corneal hysteresis from the Ocular Response Analyzer further improved the prediction accuracy in LASIK.

Take-home

- Weaker corneas tend to gravitate toward the undercorrection of myopia and should be monitored for stability before an enhancement procedure is performed.
Finding an option with presbyopia-correcting IOLs

Device used in ‘borderline’ postkeratorefractive patients

By Cheryl Guttman Krader, BS, Pharm; Reviewed by Arthur B. Cummings MD

THOUGH A HISTORY of keratorefractive surgery has generally been considered a contraindication to implantation of a presbyopia-correcting IOL, the landscape appears to be changing, according to findings of a survey of surgeons.

According to Arthur B. Cummings, MD, consultant eye surgeon and medical director, Wellington Eye Clinic, Dublin, Ireland, patients who have previously undergone keratorefractive procedures and enjoyed the benefits of good vision demand similar results after IOL surgery.

“But cataract surgery can unmask aberrations that can be present in the cornea or caused by an abnormal tear film, putting these patients at risk for reduced quality of vision,” he added.

Dr. Cummings sought to identify current practices for using presbyopia-correcting IOLs in patients with a history of keratorefractive surgery by sending a survey to almost 150 colleagues regarded as experts in both keratorefractive and cataract surgery. Ninety surgeons replied, and their responses showed that approximately two-thirds were using presbyopia-correcting IOLs in this challenging population, and the majority of those users were satisfied with the outcomes.

Additional data collected in the survey indicated that greater use of presbyopia-correcting IOLs in patients with a history of keratorefractive surgery was supported in part by the availability of new IOL technology and surgeon confidence gained from careful patient selection.

“When considering whether or not a patient is a good candidate for a presbyopia-correcting IOL, evaluation of corneal optics (i.e., higher order aberrations) and the state of the corneal surface were key,” Dr. Cummings said. “Patient personality, realistic expectations, and motivation also came forth as important issues.”

Among the surgeons who were not using presbyopia-correcting IOLs in patients with a history of keratorefractive surgery, poor past experience was the leading reason. Comments, however, brought forth the importance of considering each case individually with particular attention to corneal optics, the condition of the ocular surface, and patient personality.

According to Dr. Cummings, opinions were mixed on whether better outcomes could be achieved in patients who had undergone keratorefractive surgery for myopia versus hyperopia. The level of correction was considered when deciding to use a presbyopia-correcting IOL in hyperopes—patients with a lower amount of hyperopia were generally preferred—whereas patients who had high myopia were not more likely to be excluded than their counterparts with low to moderate myopia.

IOl Preferences

Given a list of IOL design types, the surgeons’ responses indicated that their most satisfactory results overall were achieved using the pinhole optic IOL (IC-8, AcuFocus) followed by trifocal lenses.

“The survey responses indicated that good results could be achieved with all presbyopia-correcting IOL designs,” Dr. Cummings noted. Corresponding with the preference for the pinhole optic IOL, data from the Australian IC-8 IOL SHARE study showed that the IC-8 IOL was chosen more often than all other presbyopia-correcting IOLs combined in eyes with irregular corneas.

“The IC-8 accounted for more than half of the presbyopia-correcting lenses implanted in eyes with irregular corneas, but it was also used in 20% of all normal eyes receiving a presbyopia-correcting IOL,” Dr. Cummings concluded.

Take-Home

Cataract surgeons appear to have growing confidence using presbyopia-correcting IOLs in patients with a history of keratorefractive surgery.

Conclusion

Dr. Dupps pointed out that the usual bridging collagen fibrils in the anterior stroma that contribute to this strength appear to be reduced or absent in keratoconus. OCE measurements performed by his research group in keratoconus patients show significantly lower anterior-to-posterior stress measurements in keratoconic eyes compared with normal eyes. If similar anterior weakness is an early manifestation of keratoconus, the relative advantage of SMILE may be reduced in such eyes.

“Smaller corneas tend toward undercorrection of myopia and should be monitored for stability before an enhancement procedure is performed,” he said. “SMILE has a structural advantage over LASIK in normal corneas, but PRK may be superior in the presence of occult anterior weakness.”

Dr. Dupps also noted that cloud-based, 3D patient-specific structural simulations are becoming available for highly individualized clinical-decision support.

“Emerging methods for measuring spatially resolved properties may help further individualize risk assessment and treatment optimization,” he concluded.
FEEL THE THRILL

Break free from tradition.
Unleash the power of the PanOptix® IOL.
Corneal ectasia: Effects of epi-on and epi-off CXL

Fine-tuning of procedure produces better end results for patients

By Lynda Charters; Reviewed by Karolinne M. Rocha, MD, PhD

THE CHANGES TO the eye caused by ectasia are profound and comprehensive—with shape, structure, strength, and sight affected.

In advanced disease, the changes in corneal shape are marked and the clinical findings are visible during slit-lamp evaluation. The corneal structure is affected extensively by significant epithelial hyperplasia that fills the space and compensates for the characteristic stromal loss. Biomechanical changes occur early in the disease process and are essential for determining the corneal geometric and optical properties. Finally, progressive disruptions in sight are manifested clearly by the worsening of the point spread function on topographic evaluation, according to Karolinne M. Rocha, MD, PhD, assistant professor of ophthalmology, and director, corneal and refractive surgery, Storm Eye Institute, Medical University of South Carolina, Mount Pleasant, SC.

AcrySof® IQ PanOptix® Family of Trifocal IOLs Important Product Information

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

INDICATIONS: The AcrySof® IQ PanOptix® Trifocal IOLs include AcrySof® IQ PanOptix® and AcrySof® IQ PanOptix® Toric IOLs and are indicated for primary implantation in the capsular bag in the posterior chamber of the eye for the visual correction of aphakia in adult patients, with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing improved intermediate and near visual acuity, while maintaining comparable distance visual acuity with a reduced need for eyeglasses, compared to a monofocal IOL. In addition, the AcrySof® IQ PanOptix® Toric Trifocal IOL is indicated for the reduction of residual refractive astigmatism.

WARNINGS/PRECAUTIONS: Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient with any of the conditions described in the Directions for Use labeling. Physicians should target emmetropia and ensure that IOL centration is achieved. For the AcrySof® IQ PanOptix® Toric Trifocal IOL, the lens should not be implanted if the posterior capsule is ruptured, if the zonules are damaged or if a primary posterior capsulotomy is planned. Rotation can reduce astigmatic correction. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation. Some visual effects may be expected due to the superposition of focused and unfocused multiple images. These may include some perceptions of colored halos or starbursts, as well as other visual symptoms. As with other multifocal IOLs, there is a possibility that visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. A reduction in contrast sensitivity as compared to a monofocal IOL may be experienced by some patients and may be more prevalent in low lighting conditions. Therefore, patients implanted with multifocal IOLs should exercise caution when driving at night or in poor visibility conditions. Patients should be advised that unexpected outcomes could lead to continued spectacle dependence or the need for secondary surgical intervention (e.g., intraocular lens replacement or repositioning). As with other multifocal IOLs, patients may need glasses when reading small print or looking at small objects. Posterior capsule opacification (PCO) may significantly affect the vision of patients with multifocal IOLs sooner in its progression than patients with monofocal IOLs. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure, available from Alcon, informing them of possible risks and benefits associated with the AcrySof® IQ PanOptix® Trifocal IOLs.

ATTENTION: Reference the Directions for Use labeling for each IOL for a complete listing of indications, warnings and precautions.
Topography devices + cloud technology float together

Technology evolving to include smaller, portable, smartphone-based options

By Lynda Charters; Reviewed by Stephen D. Klyce, PhD, FARVO

Corneal topography can be measured using a number of different devices, the most frequently used of which is a circular Placido device. Current Placido devices include a large-disc instrument (Keratograph 5M, Oculus), and a cone-shaped Placido device (Medmont E300, Medmont International) that fits well in the eye socket, providing broader coverage of the corneal topography.

The Placido devices also have undergone a modification of the circular device to one that provides a grid pattern, e.g., the Cassini topographer (i-Optics) and the iDesign (Johnson & Johnson Vision) that eliminate some possible errors that can occur during corneal curvature reconstruction.

The Cassini topographer also uses the second Purkinje image reflected from the posterior corneal surface, from which an estimate of the posterior corneal astigmatism can be obtained, according to Stephen D. Klyce, PhD, adjunct professor of ophthalmology, Icahn School of Medicine at Mount Sinai, NY.

Optical coherence tomography (OCT) is a future option for measuring the corneal tomography. Swept-source OCT is an evolving technology for the measurement of epithelial and corneal thickness as well as anterior and posterior surface curvatures of the cornea. Slit-scan devices, the Scheimpflug instruments, also have become a corneal tomography standard for measuring pachymetry as well as anterior and posterior corneal curvatures, he noted.

Corneal topographers and tomographers have been evolving to include additional technologies. Two such instruments are the VX120 (Visionix) and the OPD-Scan III (Nidek), which add wavefront aberrometry to Placido topography, plus Scheimpflug tomography in the case of the VX120.

Other Placido topography devices have combined rotating Scheimpflug slits to measure both corneal surfaces along with pachymetry. Examples of these instruments are the Galilei G4 (Ziemer), Sirius (CSO), and TMS-5 (Tomey).

A recent capability that has been added is the ability to measure axial length, as seen in the Aladdin HW3.0 (Topcon), Galilei G6 (Ziemer), and the Pentacam AXL (Oculus); the first two include Placido topography, whereas the latter implements Scheimpflug tomography. The Pentacam offers the ability to measure the axial length and includes wavefront aberrometry as well.

**FUTURE OF TOPOGRAPHY**

The technology is evolving in a different direction, what could be considered more practical topographic technologies are in the pipeline. These are smaller, portable, and smartphone- and cloud-based, Dr. Klyce explained.

These topographers will sit on a slit lamp and send data to the cloud. The Delphi smartphone-based corneal topography system from Intelligent Diagnostics is pending FDA approval.

“The optics of the Delphi unit are amazing,” Dr. Klyce said. The system uses a more sensitive camera than the Magellan system to obtain much finer detail in the center of the cornea. The central ring of the Delphi is 230 μm in diameter compared with the Magellan, which is 500 μm in diameter.

The Delphi system includes an auto-capture system. After the image is captured and the color-coded map is verified, the image is sent to the cloud server where higher-level calculations are performed for the various types of displays.

All displays are available remotely to the provider using any device with a web browser.

“A major advantage of putting all the data in the cloud is that multiple devices can be placed all over the world and all can send data to the cloud to form a large database of several hundred thousand examinations that in turn can be used for big data analyses for the development—using artificial intelligence—of smarter screening algorithms,” Dr. Klyce noted.

There are other advantages of data storage in the cloud, one the use of corneal topography as one factor in tele-ophthalmology. Another advantage is the possibility of virtual corneal topography screening. A consideration is that most current topography diagnostic systems were trained to only differentiate keratoconic corneas from normal corneas.

The topographers and tomographers that are available today have a growing number of capabilities: pachymetry, wavefront aberrometry, pupillometry, air puff tonometry, auto-refraction, screening programs, IOL biometry, cataract grading, dry eye parameters, and contact lens fitting.
Risuteganib—a small, synthetic, arginine-glycine-aspartate class peptide with a molecular weight of 0.75 kD and a retinal half-life of 21 days—is designed to regulate integrin functions, he explained.

A number of preclinical studies of the molecule have been conducted in the United States and Mexico have confirmed the drug’s anti-inflammatory component via the C3 receptor, reduced mitochondrial reactive oxygen species, and improved mitochondrial bioenergetics and cellular viability, according to Dr. Boyer.

The activity of risuteganib blocks oxidative stress in RPE cells and through that action ultimately eliminates photoreceptor and RPE degeneration and inflammation. “Because of this, it is a natural to look at this drug for the treatment of dry AMD,” Dr. Boyer said.

CLINICAL STUDY

The safety and efficacy of 1.0 mg of risuteganib intravitreal injections was evaluated in a study population with intermediate non-exudative AMD.

The primary endpoint was the percentage of patients that gained eight or more letters of best-corrected visual acuity (BCVA) compared with sham treatment. That particular endpoint was chosen because more than a five letter gain is considered a real clinical change in dry AMD in patients with a BCVA exceeding 20/100. “A gain of eight letters would be considered substantial,” Dr. Boyer noted.

Patients were included in the study who had dry AMD with a BCVA ranging between 33 and 72 Early Treatment Diabetic Retinopathy Study letters (Snellen range 20/40 to 20/200), and who had a symptomatic decrease in BCVA during the previous 12 months.

Patients had to have a combination of RPE disturbances and/or one or more large drusen greater than 125 μm and/or multiple intermediate drusen in the range of 62 to 124 μm in the macula. Other criteria were preserved areas of RPE and defined RPE and an outer segment ellipsoid line seen on optical coherence tomography within the central 1 mm of the macular.

The double-masked sham-controlled study was conducted at six sites in the United States, with 25 patients (16 women) were treated with risuteganib 1.0 mg and 14 (11 women) sham-treated at baseline. Most patients were Caucasian; the mean age in the sham group was 78.8 years and in the treatment group 75.9 years. The BCVA and the low-luminance BCVA were well matched in both groups. The readout was set for 12 weeks after treatment, but at 16 weeks each group received one additional injection. In the patients who received active treatment, the readout was baseline to 12 weeks versus the readout from baseline to 28 weeks, Dr. Boyer described.

RESULTS

“The results showed that the primary endpoint, was met by risuteganib in 48.0% of patients from baseline to week 28 compared with 7.1% in the sham group from baseline to week 12, a difference that reached sig-

take-home

◗ With the development of risuteganib, a treatment for dry AMD may be on the horizon.

◗ For more cutting-edge advances, go to ModernRetina.com
DARPin molecule reducing wet AMD treatment burden for patients

Option encouraging as win-win solution

By Lynda Charters; Reviewed by Rahul N. Khurana, MD

THE TWO-YEAR RESULTS of the CEDAR and SEQUOIA phase III clinical trials, among the largest clinical trials ever to study neovascular age-related macular degeneration (AMD), showed that patients did as well on the less-frequent dosing of abicipar pegol (Allergan) as they did when receiving monthly treatment with ranibizumab (Lucentis, Genentech).

According to the study, the patients were able to maintain visual gains with abicipar pegol as well as they did with ranibizumab.

“At the 2-year end point, 93% of patients treated with abicipar every eight weeks after three loading doses or six injections in the second year had stable vision, 90% of patients treated with abicipar every 12 weeks after two loading doses or four injections during the second year had stable vision, and 94% of patients treated with ranibizumab every 4 weeks or 12 injections in the second year had stable vision,” said Rahul N. Khurana, MD, clinical associate professor in ophthalmology, University of California Medical Center, San Francisco and Partner at Northern California Retina Vitreous Associates, Mountain View, CA.

A major plus associated with abicipar pegol was that the drug is nottable for its substantially decreased treatment burden, as demonstrated by those results.

“Over the course of 2 years, patients receiving abicipar pegol averaged 10 injections compared with 25 injections with ranibizumab and had the same visual outcomes,” Dr. Khurana said.

In addition to the sustained improvements in vision, the retinal anatomy improved during the second year of the study with a decrease of 147 μm in the patients who received abicipar every eight weeks, a decrease of 146 μm in the patients who received abicipar every 12 weeks, and a comparable decrease of 142 μm in the patients treated with ranibizumab every four weeks, he noted.

DRY AMD

(Continued from page 12)

nificance (p = 0.013),” according to Dr. Boyer.

The secondary endpoint, the proportion of patients with an eight or more gain in letters from baseline at crossover at week 16, showed that the percentage of sham-treated patients who met that target was double that, 14.3%, compared with 7.1% from baseline to week 12. In the active-treatment group, 20% of patients met the endpoint from baseline to week 12. That increased to 48.0% from baseline to week 128.

A subgroup of patients, eight (32.0%) of 25, in the active-treatment group gained 10 or more letters, and five (20.0%) of 25 gained 15 or more letters. In the sham-treated group, 1 (7.1%) of 14 patients achieved a 10 or higher gain in letters, and none gained 15 or more letters.

A comparison of a sham case with an active-treatment case was interesting. The former gained 6 letters of vision from baseline to week 12. However, the microperimetry deteriorated. In contrast, active treatment results in an increase of nine letters but an improvement in microperimetry was evident.

Dr. Boyer said risuteganib is a small synthetic peptide that regulates integrin functions involved in the pathogenesis of dry AMD.

“When compared to sham treatment, risuteganib met the primary study endpoint of the proportion of patients who gain eight or more letters of vision,” he concluded. “The phase II study also showed that drug had a good safety profile. An additional 1,200 injections administered outside of the study also were associated with an acceptable safety profile.”

A larger trial is planned to confirm the currently described results. ■

DAVID S. BOYER, MD

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Dr. Boyer is a consultant to Allegro Ophthalmics and has an equity interest in the company.

MDRPin molecule reducing wet AMD treatment burden for patients

Option encouraging as win-win solution

MARCH 1, 2020 :: Ophthalmology Times

Special Report ) BREAKTHROUGHS IN RETINA THERAPEUTICS
Study shows similarity in anti-VEGF injection intervals for wet AMD

About 40% of eyes still need treatment more often than every 8 weeks at end of 1 or 2 years

By Mathew W. MacCumber, MD, PhD; Special to Ophthalmology Times®

ANTI-VASCULAR endothelial growth factor (VEGF) injections are widely used in the United States for the treatment of neovascular (wet) age-related macular degeneration (AMD).

Given the treatment burden of injecting these drugs on a monthly or every-other-month schedule as initially recommended, the vast majority of U.S. retina specialists have moved to treat-and-extend regimens, the effectiveness of which is supported by the literature.1,2

In an ideal world, that would likely mean anti-VEGF injections would be given every month for a few months after the initiation of therapy, followed by longer durations, for a total of six to eight injections in the first year and fewer injections in subsequent years.

In clinical practice, several factors may prevent strict adherence to the intended schedule, including the basic biology of the disease in individual patients, physician factors (training, office scheduling), patient factors (concomitant health issues, difficulty with travel or family support, etc.) and health system factors (insurance constraints).

With the widespread adoption of the American Academy of Ophthalmology’s IRIS Registry (Intelligent Research in Sight), it is now possible to analyze the real-world injection intervals of patients in the United States with wet AMD who are treated with anti-VEGF agents.

Since its launch in 2014, the IRIS Registry has rapidly become an extremely comprehensive data resource, with 274 million patient visits representing 63 million patients and more than 15,000 ophthalmologists.

In fact, there is so much data in the IRIS Registry that it requires so...
Amid a treatment approach, San Francisco-based Verana Health—the data curation and analytics partner for the IRIS Registry—was founded by ophthalmic industry leaders to help physicians improve patient care through the power of big data. The company is helping the academy and researchers like me derive new insights and accelerate clinical research. Through Verana Practice Insights, individual ophthalmologists can get an aggregate view of physician practice trends and benchmark their individual clinical-care patterns relative to a cohort of their peers.

**WET AMD STUDY**

In collaboration with Novartis and Verana Health, my colleagues and I recently evaluated real-world injection intervals in treatment-naive patients with wet AMD. The analysis included records for eyes with a diagnosis of wet AMD, at least one anti-VEGF injection during the study period (July 1, 2013 to Nov. 2, 2017) and no anti-VEGF treatments during the six months (baseline period) preceding the first injection date (index date). Additionally, all eyes had to have had at least hand-motion vision during the baseline period and no record of other conditions that can be treated with anti-VEGF agents (e.g., diabetic macular edema or retinal vein occlusion).

The survey also ensured it excluded patients who may have impacted the findings.

Out of more than 1.7 million patients who received anti-VEGF injections during the study period, many thousands were excluded because they were already being treated with anti-VEGF therapy, or because they had diagnoses other than wet AMD. In all, records for 56,672 eyes of 54,392 patients met the criteria for analysis.

The mean age of the patients was 81.1 ± 8.4 years and nearly 65% were female. Visual acuity at baseline was distributed around 20/80, as we have seen in other studies. About one-quarter of the eyes had worse than 20/200 acuity at baseline, which highlights the need for earlier diagnosis and initiation of treatment.

Injection intervals were determined for all eyes and compared with those treated with the branded anti-VEGF therapies available during the study period: aflibercept (Eylea, Regeneron, n = 13,467 eyes) and ranibizumab (Lucentis, Genentech, n = 9,128 eyes).

### STUDY RESULTS

The mean number of injections per eye was about five per year. There was little apparent difference between Year 1 and Year 2 of treatment, among patients that received treatment within a given year, or between the two branded anti-VEGF agents studied. All in all, this is fewer injections annually than we might have expected.

When we looked only at eyes that were treated with one drug at the beginning and end of a full year (or two years), we found wide variation in injection intervals.

We would expect the injection interval to be short during the initial months of treatment, and longer after the physician uses a treat-and-extend treatment approach.

Data show, however, that even by the end of Year 1, about 40% of eyes treated with all anti-VEGF medications needed injections more frequently than every eight weeks, including 17% to 18% who still needed monthly injections. At two years, the pattern is remarkably similar, with minimal improvement in injection intervals, demonstrating just how chronic is this disease.

Eyes treated with the branded therapies and particularly those who received aflibercept injections, fared a little better, with lower percentages requiring treatment more often than eight weeks.

Note, however, that these results should be interpreted in light of the fact that this is a descriptive study and no formal statistical analyses were performed.

This study provides insight into the true treatment patterns of U.S. retina specialists who subjectively favor treat-and-extend protocols but may not always achieve that in practice.

More work is needed to correlate treatment outcomes with injection intervals. As a researcher, I am excited about the implications of partnering with the IRIS Registry for future studies.

This tremendous volume of objective data provides an opportunity to better understand current treatment patterns as we explore new approaches to AMD.

**Editor’s Note:** This article was adapted from Dr. MacCumber’s presentation at the American Academy of Ophthalmology 2019 annual meeting, and includes data compiled prior to the FDA approval of brolucizumab (Beovu, Novartis).

**REFERENCES**


Dosage & Administration: BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first 3 doses, followed by 1 dose of 6 mg (0.05 mL) every 8-12 weeks.

INDICATIONS AND USAGE
BEOVU® (brolucizumab-dbll) injection is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
BEOVU is contraindicated in patients with ocular or periocular infections, active intraocular inflammation or known hypersensitivity to brolucizumab or any of the excipients in BEOVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CST=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; IRF=intraretinal fluid; Q8=treatment every 8 weeks; Q12=treatment every 12 weeks; SRF=sub-retinal fluid.
For patients with wet AMD

THEIR VISION IS A WORK OF ART

In 2 head-to-head trials vs aflibercept, BEOVU:\1:\2:\
\• \ **Achieved** similar mean change in BCVA at Week 48\*\n\• \ **Started** eligible patients on Q12 immediately after loading, and **maintained** over half at Week 48 (56% and 51%)\1:\2†
\• \ **Demonstrated** greater CST reductions and fewer patients with IRF and/or SRF as early as Week 16, and at Week 48\‡\n
In HAWK, superior CST reductions and reductions in the percentage of patients with IRF and/or SRF were achieved at Week 16 and Week 48. In HARRIER, \(P\) values are nominal and not adjusted for multiplicity.\2 Clinical significance has not been established. No conclusions of efficacy may be drawn.

**IMPORTANT SAFETY INFORMATION (cont)**

**WARNINGS AND PRECAUTIONS**

**Endophthalmitis and Retinal Detachments**

Intravitreal injections, including those with BEOVU, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering BEOVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

\*The primary endpoint was to demonstrate efficacy in mean change in BCVA from baseline at Week 48, measured by ETDRS letters. BEOVU (Q8/Q12) demonstrated noninferiority in BCVA to aflibercept 2 mg (fixed Q8).\1

\1 In HAWK and HARRIER, respectively. All remaining patients were on Q8. Patients on BEOVU could be adjusted from Q12 to Q8 at any disease activity assessment.\1\2

\2 CST reductions in patients on BEOVU vs aflibercept at Week 16 in HAWK (\(P=0.0008\)): -161.4 \(\mu\)m vs -133.6 \(\mu\)m; Week 48 (\(P=0.0012\)): -172.8 \(\mu\)m vs -143.7 \(\mu\)m. CST reductions in patients on BEOVU vs aflibercept at Week 16 in HARRIER (\(P<0.0001\)): -174.4 \(\mu\)m vs -134.2 \(\mu\)m; Week 48 (\(P=0.0001\)): -193.8 \(\mu\)m vs -143.9 \(\mu\)m. Percentage of patients with IRF and/or SRF as early as Week 16, and at Week 48\‡

Contact your local Novartis Sales Specialist or learn more at BEOVUhcp.com
Visual gains achieved with BEOVU were similar to aflibercept

Primary endpoint: Mean change in BCVA with BEOVU vs aflibercept from baseline to Week 48

The primary endpoint was to demonstrate efficacy in mean change in BCVA from baseline at Week 48, measured by ETDRS letters. Both studies confirmed the hypothesis of noninferiority at Week 48 with a margin of 4.0 letters.

Study design: The safety and efficacy of BEOVU were assessed in 2 randomized, multicenter, double-masked, active-controlled, 2-year, Phase III studies in patients with wet AMD (N=1459). The primary endpoint demonstrated noninferiority in mean change in BCVA from baseline to Week 48 vs aflibercept as measured by ETDRS letters. Patients were randomized to either BEOVU 6 mg or aflibercept 2 mg (Q8 per label). Disease Activity Assessments (DAAs) were conducted throughout the trial at prespecified intervals. After 3 initial monthly doses, treating physicians decided whether to treat each patient on a Q8 or Q12 interval guided by visual and anatomical measures of disease activity, although the utility of these measures has not been established. Patients with disease activity at Week 16 or at any DAA could be adjusted to Q8 for the remainder of the study.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection including with BEOVU. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the BEOVU clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms.

ADVERSE REACTIONS

Serious adverse reactions including endophthalmitis, retinal detachment, increases in intraocular pressure, and arterial thromboembolic events have occurred following intravitreal injections with BEOVU.

The most common adverse events (≥5% of patients) with BEOVU were vision blurred, cataract, conjunctival hemorrhage, vitreous floaters and eye pain.


Learn more at BEOVUhcp.com
Greater CST reductions²

Secondary endpoint: CST reductions with BEOVU vs aflibercept from baseline to Week 48³

In HAWK, superior CST reductions were achieved at Week 16 and Week 48. In HARRIER, P values are nominal and not adjusted for multiplicity.² Clinical significance has not been established. No conclusions of efficacy may be drawn.

Fewer patients with IRF and/or SRF²

Secondary endpoint: % of patients on BEOVU with IRF and/or SRF vs aflibercept at Weeks 16 and 48³

In HAWK, superior reductions in the percentage of patients with IRF and/or SRF were achieved at Week 16 and Week 48. In HARRIER, P values are nominal and not adjusted for multiplicity.² Clinical significance has not been established. No conclusions of efficacy may be drawn.

IMPORTANT SAFETY INFORMATION (cont)

ADVERSE REACTIONS (cont)

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEOVU. Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEOVU. Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during dosing with BEOVU. The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEOVU is not known.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following page.
BEVOU® (brolucizumab-dbll) injection, for intravitreal injection

Initial U.S. Approval: 2019

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

1 INDICATIONS AND USAGE

BEVOU® is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

BEVOU is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

BEVOU is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

BEVOU is contraindicated in patients with known hypersensitivity to brolucizumab or any of the excipients in BEVOU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with BEVOU, have been associated with endophthalmitis and retinal detachments [see Adverse Reactions (6.1)]. Proper aseptic injection techniques must always be used when administering BEVOU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [see Dosage and Administration (2.4) in the full prescribing information].

5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection including with BEVOU [see Adverse Reactions (6.1)]. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately [see Dosage and Administration (2.4) in the full prescribing information].

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the BEVOU clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms [see Clinical Studies (14.1) in the full prescribing information].

6 ADVERSE REACTIONS

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

- Hypersensitivity [see Contraindications (4.3)]
- Endophthalmitis and Retinal Detachments [see Warnings and Precautions (5.1)]
- Increase in intraocular pressure [see Warnings and Precautions (5.2)]
- Thromboembolic Events [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 1088 patients, treated with brolucizumab, constituted the safety population in the two controlled neovascular AMD Phase 3 studies (HAWK and HARRIER) with a cumulative 96 week exposure including with BEVOU. The safety population includes 730 patients treated with brolucizumab, and 730 patients treated with the recommended dose of 6 mg [see Clinical Studies (14.1) in the full prescribing information].

Adverse reactions reported to occur in ≥ 1% of patients who received treatment with BEVOU pooled across HAWK and HARRIER, are listed below in Table 1.

Table 1: Common Adverse Reactions (≥ 1%) in the HAWK and HARRIER wet AMD Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>BEVOU (N = 730)</th>
<th>Active Control (aflibercept) (N = 729)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal detachment</td>
<td>1%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Abnormal sensation in eye</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Detachment of retinal pigment epithelium</td>
<td>1%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

*Including vision blurred, visual acuity reduced, visual acuity reduced transiently and visual impairment.

*Including anterior chamber cell, anterior chamber flare, anterior chamber inflammation, chorio-retinitis, eye inflammation, iridocyclitis, iritis, uveitis, vitreous haze, vitritis.

*Including uveitis, rash, pruritus, erythema.

*Including blindness, blindness transient, amaurosis, and amaurosis fugax.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEVOU. The immunogenicity of BEVOU was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to BEVOU in immunooassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BEVOU with the incidence of antibodies to other products may be misleading.

Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment-naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEVOU. Intraocular inflammation was observed in 8% of patients with anti-brolucizumab antibodies detected during dosing with BEVOU.

The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEVOU is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BEVOU administration in pregnant women.

Based on the anti-VEGF mechanism of action for brolucizumab [see Clinical Pharmacology (12.1) in the full prescribing information], treatment with BEVOU may pose a risk to human embryo-fetal development. BEVOU should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%–4% and of miscarriage is 15%–20% of clinically recognized pregnancies.

Data

Animal Data

VEGF inhibition has been shown to cause malformations, embryo-fetal resorption, and decreased fetal weight. VEGF inhibition has also been shown to affect follicular development, corpus luteum function, and fertility.

8.2 Lactation

Risk Summary

There is no information regarding the passage of brolucizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are transferred in human milk and because of the potential for absorption and adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least one month after the last dose when stopping treatment with BEVOU.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Females of reproductive potential should use highly effective contraception (methods that result in less than 1% pregnancy rates) during treatment with BEVOU and for at least one month after the last dose when stopping treatment with BEVOU.

Infertility

No studies on the effects of brolucizumab on fertility have been conducted and it is not known whether brolucizumab can affect reproductive capacity. Based on its anti-VEGF mechanism of action, treatment with BEVOU may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of BEVOU in pediatric patients has not been established.

8.5 Geriatric Use

In the two Phase 3 clinical studies, approximately 90% (978/1089) of patients randomized to treatment with BEVOU were ≥ 65 years of age and approximately 60% (648/1089) were ≥ 75 years of age.

No significant differences in efficacy or safety were seen with increasing age in these studies.

No dosage regimen adjustment is required in patients 65 years and above.

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T2019-105
Glare, halos reduced with modular curvature-changing fluid IOL

IOL giving surgeons option in treatment of presbyopia with better results

By Lynda Charters; Reviewed by Eric Donnenfeld, MD

A novel IOL (Juvene, LensGen), not yet available in the U.S., in addition to providing 3 D of accommodation, mimics the crystalline lens and fills the capsular bag, resulting in good stability and little posterior capsular opacification.

Considering the frequency of cataract surgeries performed worldwide, Eric Donnenfeld, MD, explained, there is a niche that needs to be filled with an IOL that addresses presbyopia and astigmatism, is stable postoperatively, and has high-quality optics with the potential to be upgraded in the face of technologic evolutions.

**HOW IT WORKS**
The silicone base lens of the IOL is implanted into the capsular bag and the refractive lens is on top of the base lens in a two-part procedure.

“As contraction occurs, fluid (silicone) fills the refractive component and causes bulging of the lens, creating accommodation,” said Dr. Donnenfeld, founding partner, Ophthalmic Consultants of Long Island and Connecticut, clinical professor of ophthalmology at New York University, and a trustee of Dartmouth Medical School, Hanover, NH.

The advantages associated with a mechanism such as this is that the IOL creates a stable effective lens position and the capsular bag does not contract, making the refraction stable as well as reducing the vitreoretinal traction and lowering the risk of floaters postoperatively. The rotation of the IOL is minimal, and posterior capsular opacification is minimal to none, he explained.

**SURGICAL EXPERIENCE**
Dr. Donnenfeld performed his first case of implantation of the IOL in March 2018 in the Dominican Republic with Juan Batlle, MD.

For Dr. Donnenfeld, a benefit of this IOL is that a standard phacoemulsification procedure can be performed without adjustments made for the IOL. The surgery is performed through a 2.4-mm incision followed by wound enlargement to 2.9 to 3.0 mm.

“After completing the cataract surgery, the wound is enlarged slightly, a viscoelastic agent is injected to fill the anterior chamber, and the silicone base lens is placed into the posterior chamber,” he explained.

The current base lens is the fourth iteration of the lens and each in turn has been thinner and more pliable, resulting in a greater accommodative effect.

When the capsular bag is filled by the IOL, it is centered, which is followed by placement of the optic into the eye. The base lens has three areas into which the refractive lens is clipped. Once this is accomplished, the procedure is finished.

A disadvantage of other current multifocal IOLs is that despite the passage of 20 years, these IOLs are still splitting light, thus increasing glare and halos postoperatively, to provide presbyopic therapy, Dr. Donnenfeld said.

“The holy grail has always been a lens that does not split light,” he emphasized.

**THE GRAIL STUDY**
A pilot study included 54 eyes at four clinical sites outside of the United States; the patients had up to 54 months of follow-up. Following the early prototypes, the final lens design was implanted in another 54 eyes at two sites outside of the United States in the Grail Study as an IDE device. Eight surgeons performed the procedures. Data also were available from 15 cases of bilateral implantations.

The monocular defocus curve at the six-month time point in the Grail Study showed that the IOL provided about 2.5 Df add. In comparison, the Tecnis Symfony IOL (Johnson & Johnson Vision) provides slightly less accommodative power. When the Juvene IOL is implanted binocularly, about 3 D of accommodative power is achieved.

“This is real accommodation based on reading and reading speed. We have shown that there are changes in the lens architecture,” Dr. Donnenfeld said.

Evaluation of the monocular visual performance showed that all patients achieve 20/40 vision; with reading, the vision is about 20/32 in almost three-quarters of patients; 86% of patients achieve 20/40. Ninety-seven percent of patient achieve good intermediate vision of 20/40 or better.

“An important result is that all patients are spectacle free,” Dr. Donnenfeld said.

The contrast sensitivity with the Juvene IOL is identical to a normal phakic lens and significantly better than that with a multifocal IOL.

A patient satisfaction survey reflected the results, with no visual disturbances, focusing difficulties, depth perception issues reported by any of the patients.

The effective lens position was stable in 24 cases of bilateral implantation.

**ROTATIONAL STABILITY**
Grail Eyes (n=10)

Surgery to three-month visit
Average Rotation = 1.7° (± 0.9 SD)

100% ≤ 5° Rotation

(Image courtesy of Eric Donnenfeld, MD)
### RADAR

(Continued from page 1)

ear and non-linear data transformations and unsupervised machine learning that provides advanced visualization with three layers of glaucoma knowledge— including the global visual functional severity, extent of visual functional loss in the hemifields, and local patterns of visual field loss,” explained Dr. Yousefi, assistant professor, Departments of Ophthalmology and Genetics, Genomics, and Informatics, University of Tennessee Health Science Center, Memphis. “The system also provides personalized monitoring, data from thousands of previous glaucoma patients, and can identify rapid or slow progression,” he added.

Though the basis for this advanced visualization technology is highly complex, the investigators sought to develop a screen for monitoring glaucoma that is user-friendly and able to be understood by non-medical individuals. It includes more than 13,000 visual fields cross-sectionally.

“We applied principle component analysis to linearly reduce the number of dimensions and extracted the global characteristics of the visual fields,” Dr. Yousefi said. “We then applied manifold learning to grab the local patterns of visual field loss and eventually generated this to a map.”

### GLAUCOMA DATA

To make sense of the data from the collected visual fields, the investigators first identified very dense areas, and then applied unsupervised clustering to identify 32 non-overlapping clusters that represented different levels of visual field severity. According to Dr. Yousefi, when the mean deviation of each cluster was computed, the observation was that the severities of the visual fields increased moving from the top right to the bottom left of the screen.

“The AI pipeline was able to identify the global functional severity of the eyes in the various clusters, i.e., mostly normal eyes on the right and those with severe visual field loss on the left and bottom left of the screen,” he said.

The researchers also computed the glaucomatous severity in the inferior and superior hemifields.

“We noticed that the AI wisely put eyes with similar hemifield characteristics into different clusters, although statistically their global severity may have been similar,” noted Dr. Yousefi, indicating that the AI was able to differentiate similar damage in different locations and cluster those eyes together.

### TESTING TECHNOLOGY

Investigators conducted a study in which they tested a method to identify and decompose visual fields to 17 different archetype or patterns. They tried to decompose the visual fields at each cluster, Dr. Yousefi explained, to the different archetypes and then identify the dominant pattern attributable to each cluster.

“Collectively, each region of the dashboard can demonstrate global visual field loss, the extent of visual field loss in the hemifields, and local patterns of visual field loss,” he said.

Because of the capabilities of the radar, the technology can be used for personalized glaucoma monitoring, retention of the history of previously monitored patients, and identification of rapidly and slowly progressing eyes.

The availability of this information allows clinicians to easily adjust treatment regimens based on the glaucoma trajectory in a given patient’s eyes; clinicians will be able to adjust the treatment based on the cluster to which the patient is progressing and possibly positively impact the patient’s quality of life.

As a proof of concept, Dr. Yousefi and colleagues tracked eyes from benchmark data that indicated that the glaucoma was not progressing using 10 visual fields for each eye.

“As expected, most of the eyes did not have substantial changes in the visual fields,” he explained. “Some eyes that had visual field changes that were not in the direction of progression also were considered stable.”

Based on these data, Dr. Yousefi pointed out that the specificity of the radar was about 94%, he said. Investigators also performed the same analysis in eyes based on data from a separate algorithm that indicated that they eyes would progress. Most of these eyes showed glaucomatous changes in the direction of glaucoma worsening.

Dr. Yousefi concluded that with this method, ophthalmologists can perform better functional assessment of patients with glaucoma compared to the currently available tools.

“Advanced computational tools can provide more informative objective outcomes,” he said. “While deep learning typically generates black box and yes/no outcomes, our proposal may be helpful for developing models that can be interpreted more. Next-generation glaucoma assessment tools can provide multiple layers of glaucoma knowledge using advanced visualization.”

### TAKE-HOME

> Artificial intelligence can push the boundaries of glaucoma diagnosis and monitoring.

### PRESBYOPIA IOL

(Continued from page 21)

patients from one to six months postoperatively as well as after 54 months. The rotational stability of the IOL was also seen. In addition, there was no significant loss of endothelial cells.

After more than 4 years of follow-up there was no posterior capsular opacification.

According to Dr. Donnenfeld, the Juvene IOL is well tolerated and can be inserted through a small incision.

“This IOL has been shown to reduce capsular opacification, vitreous traction, and it fills the capsular bag, and has an exchangeable platform,” he concluded. “The early results indicated that patients gain 3 D of accommodation.”

FDA trials are expected to begin shortly. Data on those eyes with one to six months of follow-up were released.
Optometric practice is going through a lot of change, with online sales of contact lenses and prescription glasses eroding some of optometry’s traditional revenue streams.

At the same time, an aging population is leading to an increased demand for treatment of age-related eye diseases, such as cataract, glaucoma, macular degeneration, and dry eye. Given these trends, more optometrists are seeing the financial and clinical need to go beyond vision care to manage or co-manage medical conditions.

Dry eye disease presents a perfect opportunity for ophthalmologists and optometrists to work together for the benefit of our patients. There are two common situations in my practice where this occurs.

**SCENARIO 1:**
*The proactive OD*

I work with many optometrists in the surrounding community who will diagnose patients with dry eye and offer a range of treatments to address their symptoms. They may prescribe immunomodulators like Restasis (Allegan), Xiidra (Novartis), or Cequa (Sun), microwavable moisture masks, oral omega-3 supplements, lid hygiene wipes, and artificial tears.

If these measures aren’t enough or if they suspect the patient actually has impacted meibomian glands that require a procedure for evacuation, many will refer the patient to me for thermal pulsation therapy (LipiFlow, TearScience/Johnson & Johnson Vision).

I will treat the patient and send them back to their optometrist for ongoing management of their ocular surface disease, with the understanding that the patient may need a repeat LipiFlow treatment in a year or two.

To capture patient referrals like this, it is important that optometrists in your area learn about the advanced technologies you offer, both for diagnosis and for treatment. This is essential for dry eye, but also for procedures like cross-linking for keratoconus and refractive cataract surgery.

We send an e-newsletter to primary-care providers and optometrists; send a practice liaison to visit practices in person; and offer educational seminars for COPE credit, as well as non-credit dinner programs that are a mix of social networking and educational reinforcement. I have found it powerful to demonstrate our technologies whenever possible at these seminars.

At a recent gathering, for example, several optometrists discovered that they had significant gland dropout on LipiView meibography, despite being asymptomatic. That experience helped to underscore the value of the diagnostic tool better than anything I could have said.

**SCENARIO 2:**
*The surgical referral who isn’t ready*

We often see patients who have been referred for cataract surgery but who turn out to have an unstable tear film that I want to address before surgery. The patient may have

**Continues on page 24: Village**
INFLAMMATORY

(Continued from page 1)

“I tell patients who present with orbital inflammation that we may be at the beginning of a journey with a path we will walk together to better define their disease so that we can tailor the treatment,” she said.

“I tell patients who present with orbital inflammation that we may be at the beginning of a journey with a path that we will walk together to better define their disease so that we can tailor the treatment.”

Louise A. Mawn, MD

DIAGNOSTIC CHALLENGE

Orbital inflammation can develop in association with several diseases, including infectious entities, structural problems, autoimmune disorders, and neoplastic diseases. It may also be idiopathic.

“If I call the inflammation idiopathic, however, I tell patients that we learned in medical school that the idiots do not know the pathology, and that I will continue to give vigilant attention to their disease because it may be in evolution,” Dr. Mawn said. “We only apply the term ‘nonspecific orbital inflammation’ to describe a condition after we have exhaust ed a search for a specific cause.”

Diagnosis in patients with OID involves a complete review of systems and physical examination, a laboratory work-up, imaging, and “bladeless” biopsy, but tissue biopsy may also be necessary. The review of systems homes in on identifying symptoms of joint, gastrointestinal, sinonasal, and skin disease, as well as any personal or family history of endocrine or immune disease. The evaluation also includes a drug history, recognizing that some medications (e.g., bisphosphonates and propylthiouracil) can cause orbital inflammatory reactions.

A CT scan is generally performed as initial imaging because of ease of access and lower cost compared with MRI. Patients with orbital inflammation may present first to the emergency department where a CT scan may be done.

MINIMIZING MORTALITY

Regardless of the etiology of the inflammation, the immune mediators causing the inflammation are the same. Options for controlling the immune response include agents that act via non-specific pathways and biology that have specific targets. Treatment selection, however, may be dictated by insurance, considering that some third-party payers require using a step-step approach to treat inflammatory disease.

“We may have to start with steroids, which are the least expensive option, then ramp up to other non-specific immune modulators before moving to specific agents,” Dr. Mawn said.

Steroids are the mainstream of medical management for OID. They act throughout the body and have multiple possible systemic side effects. Baseline evaluations and monitoring require checking body weight, blood pressure, a complete blood count, a complete metabolic profile with lipids, and ruling out tuberculosis.

“Our goal using steroids is to use the lowest effective dose that will resolve the inflammation for the minimum period of time to avoid side effects,” Dr. Mawn said.

Other non-specific immune modulators used to treat OID include methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine. Dr. Mawn said that methotrexate is another cornerstone of medical management for OID, but it is also associated with a number of side effects.

“The immunomodulatory action of methotrexate is mediated by inhibition of dihydrofolate reductase that leads to depletion of folic acid,” she said. “Many of the side effects of methotrexate can be mitigated by treating patients with 1 mg/day of folic acid.”

Dr. Mawn added that because methotrexate is stored in the liver, some physicians advocate against giving it to patients who use alcohol or who are on other medications that affect their liver.

Treatment with a specific immunomodulator often starts with an agent that targets tumor necrosis factor-alpha (e.g., etanercept, infliximab, adalimumab). Other biologics, which tend to be more expensive and therefore are reserved for later use, include rituximab, a monoclonal antibody that targets CD20 on B cells and B cell precursors. Baseline testing for patients who are to be started on rituximab should include a complete blood count with differential and platelets, complete metabolic profile, and serology for hepatitis A, B, and C and HIV.

Other biologics that might be considered for treating OID include tocilizumab, which targets interleukin-6.

Teprotumunab is an investigational fully human monoclonal antibody targeting the insulin-like growth factor-1 receptor (IGF-1R) that is being evaluated for the treatment of active inflammatory thyroid eye disease.

TAKE-HOME

Corticosteroids and a variety of other non-specific and specific immunomodulatory drugs are used in the medical management of orbital inflammatory disease. Establishing a diagnosis guides targeted patient care.

VILLAGE

(Continued from page 23)

a positive MMP-9 test, abnormal osmolarity, and moderate to severe meibomian gland dropout—but it may be the first time they have been told they have dry eye. This can be a tricky situation that calls for diplomacy.

I tell the patient that we have specialized equipment that specifically checks for dry eye disease. “Not all practices have this technology, so that’s why Dr. Smith referred you to me,” I will tell them. “We’ll get that tear film stabilized and then we’ll be able to get more reliable measurements for surgery. When you go back to Dr. Smith after surgery, she will continue taking care of your dry eye, as well.”

This can let the patient know that their care is important. It creates a level of trust, and can help lead to a better outcome.

I also take the time to communicate directly with the optometrist and educate him or her about my findings and the treatment protocol that is needed to ensure the patient gets the best outcome from cataract surgery. As partners in the patient’s care, we both want to avoid time-consuming refractive surprises and instead have a satisfied patient with excellent visual outcomes.

Both of these scenarios are working well for our practice. What strategies have you used to promote good co-management relationships with optometrists in your region?

CYNTHIA MATOSSIAN, MD, FACS
E: cmatossian@matossianeye.com
Dr. Matossian has no relevant financial interests to disclose.
Fluorescein angiography key in diagnosing retinal diseases

Despite being older procedure, FA proving an effective tool for ophthalmologists

By Lynda Charters; Reviewed by Steven Yeh, MD

Imaging modalities have been continuously evolving over the years and becoming more powerful. Fluorescein angiography (FA) is one of the oldest procedures used by ophthalmologists, but its age does not decrease its value.

Steven Yeh, MD, described the patterns of various diseases and how FA adds to the clinical evaluations of these patients. Dr. Yeh is the M. Louise Simpson Associate Professor of Ophthalmology, Emory Eye Center, Emory University School of Medicine, Atlanta.

**BIRDSHOT RETINOCHOROIDOPATHY (BRC)**

Dr. Yeh described a 40-year-old man who complained of floaters and debris in the visual field for two years. He underwent laser retinopexy for suspected lesions. An examination showed 1+ anterior vitreous cells bilaterally, trace vitreous haze, and mild disc edema. The optic disc had some hyperfluorescence with leakage and the vessels had characteristic segmental periphlebitis. No lesions characteristic of birdshot retinochoroidopathy (BRC) were apparent in the left eye, and the segmental periphlebitis was even more prominent with leakage from the optic disc in the late frames and a retinal pigment epithelial (RPE) blush.

Indocyanine green angiography (ICGA) images showed multiple hypofluorescent lesions that define the BRC phenotype but no cystoid macular edema (CME).

“There was a paucity of lesions on FA images, but ICGA showed more lesions,” Dr. Yeh said. “It is important to pair the two technologies when this disease is suspected.”

BRC can lead to severe CME and resultant changes in visual acuity. In another patient in whom BRC developed, optical coherence tomography (OCT) showed the diffuse RPE blush bilaterally that developed because of the chronic nature of the disease. OCT also showed intraretinal and subretinal fluid and an epiretinal membrane. Local and systemic treatments resulted in improved vision.

BRC can also occur in choroidal neovascularization (CNV). A 53-year-old woman with HLA-A29+ BRC had accompanying bilateral distorted vision of 20/40 in the right eye. OCT showed the presence of subretinal hyperreflective material over a pigment epithelial detachment (PED).

Dr. Yeh explained that fluorescein still has a role in patients such as this.

“It showed hyperfluorescence in an early angiogram with leakage within the choroidal neovascular membrane and the optic disc,” he said. “This suggests that the disease has both inflammatory and neovascular components. The patient was treated with adalimumab (Humira, AbbVie) and serial anti-vascular endothelial growth factor (VEGF) injections and had a good outcome as seen on FA and OCT.

According to Dr. Yeh, CNV can occur in about 5% to 10% of BRC cases.

“The risk of CNV in these cases is not surprising because the macula is involved,” he said. “In this context, combination therapy is important.”

**ACUTE POSTERIOR MULTIFOCAL PLACOID PIGMENT EPITHELIOPATHY**

A 24-year-old woman presented to Dr. Yeh with vision loss to 20/100. Placoid lesions were seen on fundus photographs. FA showed characteristic early hyperfluorescence with a late hyperfluorescent signal throughout the posterior pole. Previously oral prednisone (60 mg/day) was started at another institution, the patient discontinued treatment, and the vision decreased to 20/100.

Imaging of the left eye showed lesions encroaching on the fovea. Early hyperfluorescence was seen with late diffuse and subtle hyperfluorescence over the lesions. Laboratory workup was negative for infectious diseases. Intravenous solamedrol was administered for 3 days; oral prednisone taper was administered. One month after treatment, the vision improved from 20/100 to 20/40 and ultimately to 20/25.

**SERPIGINOUS CHOROIDOPATHY**

A 40-year-old patient with inactive serpiginous choroidopathy presented with the complaint of a new scotoma in his right eye. The patient had been treated with cyclosporine and azathioprine. An early-phase angiogram showed some hyperfluorescence and the late-phase angiogram some staining.

Fundus autofluorescence—a key imaging modality for this disease—showed a large area of hypoautofluorescence that corresponded precisely to the fundus photograph. New imaging showed a new area of hypofluorescence and possibly some late hyperfluorescence at the lesion border. It had to be determined if this new finding needed additional treatment.

In this patient the fundus autofluorescence highlights the lesion in conjunction with FA findings.

“We found this to be a marker of disease activity,” Dr. Yeh said. “In this context FA should be used with fundus autofluorescence.”

**PUNCTATE INNER CHOROIDOPATHY (PIC)**

A 27-year-old woman with myopia had a history of punctate inner chorioidopathy (PIC) and a scotoma in the left eye. She presented with new visual distortion in the right eye. Evaluation of a subtle yellow blush was done to determine if this represented CNV or inflammation. “This is a case in which FA comes in handy,” Dr. Yeh noted.

The venous-phase angiogram was unremarkable, but the late-phase images showed diffuse punctate hyperfluorescence with leakage.

“We interpreted this as an active inflammatory lesion that was treated with prednisone (1 mg/kg) tapered over the course,” he said.

The patient was followed with fundus photography and OCT. FA showed lesion resolution.

CNV associated with PIC is a high-risk complication that is thought to occur in from 69% to 77% of patients with PIC. “CNV is a key distinguishing feature of this disease. In these patients, FA shows early hyperfluorescence in an area of subretinal blood and late leakage from the CNV that requires anti-VEGF treatment,” he said.

In another PIC case, FA highlights the CNV well-demarcated lesion early and the PED extent in the disease.

**MULTIPLE EVANESCENT WHITE DOT SYNDROME**

This disease process is seen predominantly in women and is unilateral in 80% of cases. One-third of patients report a viral prodrome. The disease falls into an acute...
Hardware, software offering a window to cornea diagnosis

Topographers/tomographers cornerstones for evaluations of keratoconus, keratectasia

By Cheryl Gutman Krader, BS, Pharm; Reviewed by Vishal Jhanji, MD

By Cheryl Gutman Krader, BS, Pharm; Reviewed by Vishal Jhanji, MD

ADVANCES IN HARDWARE and software make corneal topography and tomography useful tools for ectasia risk screening and for the diagnosis and follow-up of keratoconus and post-LASIK ectasia, but other factors and clinical correlation are important when interpreting the findings, according to Vishal Jhanji, MD, professor of ophthalmology, University of Pittsburgh, Pittsburgh.

“Corneal topography and tomography allow precise measurement of anterior and posterior corneal curvatures and corneal thickness and enable the diagnosis, classification, and monitoring of progression of corneal diseases, but there can be more to the picture,” said Dr. Jhanji. “Hopefully, these processes will be improved in the future through a combination of biomechanical factors, topographic indices, and surgery-induced risk stratification.”

DEVICE DESCRIPTIONS

Corneal topographers analyze the pattern of light rays reflected off the cornea and tear film-air interface and reconstruct the corneal shape. Corneal tomographers evaluate the whole cornea by obtaining information from the anterior and posterior corneal surfaces to reconstruct three-dimensional images of the anterior segment.

The corneal imaging technology has continued to evolve. Initial instruments based on Placido disk technology only analyzed the central anterior surface of the cornea and only provided anterior corneal shape-based indices. Subsequently, scanning slit-based technology was introduced that also imaged the posterior cornea.

Dr. Jhanji pointed out that with information about posterior surface elevation, keratoconus began to be diagnosed more efficiently.

Scheimpflug camera-based devices were developed that could image the central anterior and posterior cornea as well as the peripheral cornea. Software for these systems was developed to generate comprehensive diagnostic indices for identifying subclinical and frank keratoconus.

CLINICAL APPLICATIONS

Because abnormal topography is arguably the most important risk factor for post-LASIK ectasia, one of the most common indications for topography/tomography in an anterior segment practice is screening for ectasia risk.

Red flags for poor surgical candidates include image-based identification of abnormalities such as an asymmetric bow tie, skewed radial axis, or inferior/paraxial steepening or thinning. In addition, different devices generate calculation-based scores (e.g., BCV index, Sirius; BAD-D score, Pentacam; KISA%, Orbscan).

“The reliability of these scores depends on the reliability of the individual factors that are used to calculate them” Dr. Jhanji said. “However, interchange between devices can lead to extrapolation errors. For that reason, it is preferable to do serial follow-up using the same device.”

TAKE-HOME

» Corneal topography and tomography have an important role as screening tools in patients seeking laser vision-correction surgery and to diagnose and follow keratoconus and other corneal ectatic disease.

LIMITATIONS OF DEVICE-BASED SCREENING

Dr. Jhanji said the risk of post-LASIK ectasia is also influenced by surgical and postsurgical factors that are not accounted for by corneal topography/tomography. These include corneal biomechanics, flap thickness variation, ablation volume and decentration, and possibly eye rubbing or IOP spikes postoperatively.

In addition, although serial imaging showing changes in individual parameters or calculated indices may be interpreted as providing a clear indication of ectasia development and progression, other factors may need to be considered for decisions about patient management.

According to the Global Consensus on Keratoconus and Ectatic Disease, consistent change in at least two of the following parameters can be used to identify progression: steepening of the anterior corneal surface, steepening of the posterior corneal surface, thinning and/or changes in the pachymetric rate of change.

The group also recognized, however, the importance of considering patient age and change in refraction. Best corrected distance visual acuity is incorporated in the ABCD Grading System for keratoconus (available on Pentacam) along with the radius of curvature of the anterior and posterior corneal surfaces and corneal thickness at the thinnest point.

“In all cases, clinical correlation is important,” Dr. Jhanji concluded. “What looks like keratoconus on a topographic map may be a change caused by other corneal pathology.”

RETAIINAL

(Continued from page 25)

Idiopathic large blind spot syndrome spectrum of disorders, Dr. Yeh explained.

FA shows early and late hyperfluorescence in areas of focal granularity and some areas of hypofluorescent lesions on ICGA images.

Dr. Yeh said FA remains a key imaging modality that shows subtle and highly characteristic patterns for BRC, acute posterior multifocal placoid pigment epitheliopathy, serpigous choridopathy, PIC, and multiple evanescent white dot syndrome that can help distinguish these disease diagnoses.

“We use FA during initial evaluations and think it is extremely valuable for diagnosing and recognizing structural complications,” he said.

In many cases, monitoring can be performed using other imaging modalities depending on the diagnosis and the secondary manifestations, according to Dr. Yeh.

“Disease recurrences and complication are also highlighted by FA findings,” he concluded. “FA remains a valuable tool for the white dot syndromes.”

STEVEN YEH, MD

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Dr. Yeh has no financial interest in the subject matter of this report.
Updates on Pharmacological Treatment of Open-Angle Glaucoma

In this video series of *Ophthalmology Times® Insights*, Joseph F. Panarelli, MD, and Sahar Bedrood, MD, PhD, examine approaches used to improve outcomes in patients with open-angle glaucoma.

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Study identifies genetic loci associated with keratoconus

Researchers hope to understand biochemical pathways disrupted in keratoconus

By Cheryl Guttman Krader, BS, Pharm; Reviewed by Bennet J. McComish, PhD

In the largest study of its kind in keratoconus published so far, researchers conducting a genome-wide association study found a region of chromosome 11 in which multiple genetic variants were significantly more common in keratoconus patients than in unaffected individuals. Functional annotation of the associated variants indicated that several of the genes in the identified locus are likely involved in apoptotic pathways.

The findings were published in the February issue of JAMA Ophthalmology [McComish BJ, et al. JAMA Ophthalmol. 2020;138(2):174-181.] Bennet J. McComish, PhD, research fellow, Menzies Institute for Medical Research, University of Tasmania, Tasmania, Australia, is lead author of the article.

“Our study, which was an international collaboration between groups in Australia, the United States, and the United Kingdom, aimed to identify genetic variants involved in the risk of developing keratoconus,” he said. “This information will allow us to better understand the biochemical pathways that are disrupted in keratoconus. It will help in the identification of potential therapeutic targets for this disease that is relatively common and can cause severe visual impairment.”

‘This information will allow us to better understand the biochemical pathways that are disrupted in keratoconus.’

– Bennet J. McComish, PhD

Dr. McComish said the region of chromosome 11 that researchers identified contains at least five protein-coding genes.

“The next step will be to determine which of those genes is implicated in the disease, recognizing that other genetic variations nearby can ‘hitchhike’ with the variants that cause the disease,” he said.

Data used for the study were collected from individuals seen between January 2006 and March 2019 at eye clinics in Australia, the United States, and Northern Ireland. First, in a discovery phase, data were analyzed from 522 Australians with keratoconus and 655 unaffected individuals representing a control group. Subjects for the control group were taken from cohorts of the Australian Blue Mountains Eye Study and a previous study of glaucoma.

Genotyping for 551,839 variants was done using the HumanCoreExome single-nucleotide polymorphism (SNP) array (Illumina). The SNPs with P values <1.00 x 10^-8 that were identified in the discovery cohort were assessed in three independent replication cohorts using the MassARRAY System (Agena Bioscience).

The replication cohorts included 818 affected subjects with keratoconus and 3,858 unaffected controls. They were comprised of individuals included in a previous keratoconus GWAS data set from the United States, a cohort of subjects with keratoconus and unaffected controls from Australia and Northern Ireland, and a case-control cohort from Victoria, Australia.

In the discovery cohort as well as in the three replication cohorts, the majority of keratoconus subjects were males (55% to 61%) and mean age for the cases in each cohort ranged from 35 to 45 years. The proportion of males among controls in the discovery cohort was greater than in the replication cohorts (47% versus ~38%). Mean age of the controls in all four cohorts was 17 to 28 years older than the mean age of their keratoconus counterparts.

The association analysis in the discovery cohort identified two novel loci with genome-wide significance. One of the novel loci was on chromosome 22 at rs138380, 2.2 kb upstream of casein kinase I isofom epsilon gene (CSNK1E). None of the SNPs in the CSNK1E locus reached significance in the replication cohorts, despite the fact that the CSNK1E locus had the strongest association in the discovery cohort. When the data from the discovery cohort and the three replication cohorts were combined, 12 SNPs at the novel PNPLA2 locus were found to be associated with keratoconus at genome-wide significance.

\[ \text{TAKE-HOME} \]

A genome-wide association study including 1,177 Australians discovered a genetic locus on chromosome 11 associated with keratoconus. The locus contains multiple variants across several genes, some of which are implicated in apoptotic pathways.

\[ \text{BIOL O G I C A L} \]

\[ \text{S I G N I F I C A N C E} \]

Discussing their findings, the researchers noted that the function of the protein encoded by the lead SNP, which was located in an intron of PNPLA2, is to catalyze the initial step in triglyceride hydrolysis. Stating that there is no obvious connection between this biochemical pathway and keratoconus, they observed that the closest gene to an association signal is not necessarily the causative gene.

“Other genes in the identified region are known to be involved in regulating apoptotic cell death, a process that has been suggested previously by other authors to be part of the mechanism underlying the development of keratoconus,” Dr. McComish said. “This finding will help focus future studies on the role of these genes in keratoconus.”

\[ \text{L I M I T A T I O N S} \]

The older mean age of the control cohorts compared to the case cohorts represents a possible study limitation. Because of the demographic difference, it will be important to assess the identified loci for age-associated effects in future studies, they wrote.

\[ \text{B E N N E T} \]

\[ \text{M C C O M I S H,} \]

\[ \text{P H D} \]

Dr. McComish has no relevant financial disclosures related to this topic.
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VERMONT

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

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

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

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

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

The University of Vermont is an Equal Opportunity/Affirmative Action Employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability, protected veteran status, or any other category legally protected by federal or state law. The University encourages applications from all individuals who will contribute to the diversity and excellence of the institution.

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ASSISTANT PROFESSOR/ASSOCIATE PROFESSOR
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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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Located in Burlington, the University of Vermont and the University of Vermont Medical Center serve as Vermont’s only academic medical center. It is the only ACS verified Level I trauma center in the state and provides tertiary care to patients from Vermont and Northern NY. Burlington is a vibrant community located on the shores of Lake Champlain, between the Adirondack and Green Mountains. With year-round recreational opportunities, safe communities and excellent schools, this progressive community has been frequently cited as one of the most livable cities in the U.S.

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POST-TREATMENT (WEEK 24)
Proptosis: 21 mm

Learn more at TEPEZZAhcp.com

INDICATION
TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Please see Brief Summary of Prescribing Information for TEPEZZA on adjacent pages.


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TEPEZZA™
treprotumumab-trbw
For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE
TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions
TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/ or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease
TEPEZZA may cause an exacerbation of preexisting bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia
Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Infusion Reactions [see Warnings and Precautions]
- Exacerbation of Inflammatory Bowel Disease [see Warnings and Precautions]
- Hyperglycemia [see Warnings and Precautions]

Clinical Trials Experience

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

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT01868997] and Study 2 [NCT03298687]), consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>TEPEZZA N=64 N (%)</th>
<th>Placebo N=66 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle spasm</td>
<td>21 (20%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (17%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (13%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (12%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (12%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>8 (10%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>8 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgusia</td>
<td>7 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (8%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>7 (8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of anti-drug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of anti-drug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor-1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There is insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero treprotumumab exposure in cynomolgus monkeys dosed once weekly with treprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Treprotumumab exposure may lead to an increase in fetal loss [see Data]. Therefore, TEPEZZA should not be used in pregnant, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA.

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of treprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the treprotumumab treated group compared to the control group. Treprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium; closely set eyes, micrognathia, pooling and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of treprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to treprotumumab may cause harm.

Lactation

Risk Summary
There is no information regarding the presence of TEPEZZA in human milk, the effects on the breastfed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA may cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Inflammatory Bowel Disease

Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/ colic, urgency, tenesmus or incontinence.

Lactation

Advise females of reproductive potential that TEPEZZA may cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

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Lake Forest, IL 60045

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INDICATIONS: Indicated for primary implantation for the visual correction of aphakia in adult patients in whom the cataractous lens has been removed. The lens is intended for placement in the capsular bag.

WARNINGS: Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient. PRECAUTIONS: Do not resterilize this intraocular lens by any method. Do not store lenses at temperatures over 43°C (110°F). Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the benefit/risk ratio before implanting a lens in a patient with conditions as outlined in the enVista IOL Directions for Use. ADVERSE EVENTS: As with any surgical procedure, there is risk involved. Potential complications accompanying cataract or implant surgery may include, but are not limited to the following: corneal endothelial damage, infection (endophthalmitis), retinal detachment, vitritis, cystoid macular edema, corneal edema, pupillary block, cyclitic membrane, iris prolapse, hypopyon transient or persistent glaucoma, and secondary surgical intervention. CAUTION: Federal law restricts this device to sale by or on the order of a physician.

ATTENTION: Reference the Directions for Use labeling for a complete listing of indications and important safety information.

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