3D printing in ophthalmology
Technology can improve outcomes for patients

By Lynda Charters; Reviewed by Andrea A. Tooley, MD

3D PRINTING FOR surgical applications is not the future of ophthalmology—it is the present, according to Andrea A. Tooley, MD.

Though ophthalmology may have been slower than other medical specialties to adopt this technology, many surgical applications are available, explained Dr. Tooley, an ASOPRS fellow at Columbia University and Manhattan Ear, Eye, and Throat Hospital, New York, and assistant professor of ophthalmology, Mayo Clinic, Rochester, MN.

3D printing is also known as additive manufacturing, in contrast to subtractive technology or the use of molds. The most common type of 3D printing is the liquid form, which uses thin layers of a liquid polymer that is cured rapidly by ultraviolet light to facilitate the addition of new overlying layers to create the desired shape.

This is the primary use in medical applications and is referred to as stereolithography, Dr. Tooley explained.

Continues on page 11: 3D Printing

Seeking the holy grail treatment to tackle endophthalmitis head-on

Anti-infective delivery systems must overcome barrier, elimination challenges

By Lynda Charters; Reviewed by Irmgard Behlau, MD

Various approaches have been developed to treat endophthalmitis, including topical and systemic drugs and periocular and intravitreal injections. The noninvasive methods of topical and systemic means of delivery are the goals because of their lack of invasiveness. With injections, there is always the risk of development of endophthalmitis. However, nothing is perfect and the holy grail remains elusive, according to Irmgard Behlau, MD.

According to Dr. Behlau, research assistant professor, Tufts University School of Medicine, Tufts Medical Center, Boston, drops work if the patient has keratoendophthalmitis, but successful delivery is limited to only 1% to 7% of the drug.

Frequent instillation every one to two hours is mandatory, and the drug has to get through the natural barriers of the ocular surface and tears.

Recent advances that have been achieved are antibiotics with small molecular weights, increased residence times and

Continues on page 18: Endophthalmitis
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ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.


See the Passion in Each Patient

Johnson & Johnson VISION
Device Technology

21 CARE DELIVERY: MOTIVATING PATIENTS WITH MOBILE DEVICES
Advances in medical devices are helping ophthalmologists enhance patient care in their practices.

Clinical Diagnosis

24 NEUROTROPHIC KERATOPATHY: DIAGNOSTICS, TREATMENT MERGE
Breakthroughs in degenerative disease treatment restore corneal sensation, vision in patients.

Gene Therapy

32 COMPLICATIONS, COSTS OF GENE AND CELL-BASED THERAPY TARGETED
Researchers find two areas in need of further study before bringing to the selected patient base.

Imaging

31 OCT KEY TOOL IN DETERMINING GLAUCOMA PROGRESSION
Structural evaluation with OCT, functional testing should be used throughout the disease continuum to detect development.

Therapeutics

1 SEEKING THE HOLY GRAIL TREATMENT FOR ENDOPTHALMITIS
The latest treatment option offers versatility and plasticity, is often programmable for individualized drug delivery, and is 100% biodegradable.

15 NEW TECHNIQUES PROBED FOR MANAGING DRY EYE DISEASE
Treatments address blepharitis, meibomian gland dysfunction, aqueous deficiency.

16 LAB TEAR TESTS AID REIMBURSEMENTS, CLINICAL APPLICATION OF DRY EYE
Renewed interest in dry eye is driving research and an increasing understanding of the corneal surface's role in refractive, cataract, and glaucoma outcomes.
We are springing into March

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

As the calendar turns to March, we are preparing an issue that offers plenty of high-level content to help you get an edge in your practice.

On the cover of this issue, we look at the growing impact of 3D printing on ophthalmic surgery. Andrea A. Tooley, MD, tells us that what was once considered science fiction is now science fact. The 3D printing for surgical applications is here.

Therapeutics also is featured on the cover in this issue as we examine various approaches have been developed to treat endophthalmitis, including topical and systemic drugs and pericellular and intravitreal injections. Irmgard Behlau, MD, discusses a new option that offers versatility and plasticity.

Our therapeutics coverage also includes the first of a two-part series that takes a macro and micro look at the intersection of clinical value and financial reimbursement for eye-care diagnostics.

In surgery, we also look at options for the treatment of viral retinitis. J. Fernando Arevalo, MD, PhD, FACS, explains that when medications fail, surgery may be a treatment option. Moreover, tools such as optical coherence tomography (OCT) can be used to diagnose atrophic retinal detachments.

In this core section, we also look at the drive to end dysphotopsias in premium IOLs. With advanced formulas and improved standard lenses, ophthalmologists can correct myopia, hyperopia, and astigmatism, greatly reducing the need for glasses for distance for almost all patients with healthy eyes.

We examine the latest in device technology, as we prepare for shifts in the field sparked by advances in technologically advanced medical devices that are driving changes in patient care and impacting the lives of patients. According to Leslie S. Jones, MD, the delivery of patient care is moving into the forefront, with the focus shifting increasingly more from office-based services to mobile devices to further enhance delivery of care.

The clinical diagnosis section in this issue includes an examination of neurotrophic keratopathy. Francisco C. Figueiredo, MD, PhD, FRCophth, explains that a specific therapeutic approach is required to address the disease presentation, which is described by Mackie’s classification of three stages of severity, and the clinical presentation is always the same regardless of the etiology.

Our imaging content focuses on OCT as a tool in determining glaucoma progression. Felipe A. Medeiros, MD, PhD, tells us that structural evaluation with OCT and functional testing with visual fields should be used throughout the glaucoma disease continuum to detect progression.

Gene therapy remains a hot topic and Sophie X. Deng, MD, explains the use of confocal microscopy to obtain important diagnostic information in patients with limbal stem cell deficiency. Diagnosis can be tricky because the disease presentation varies greatly with the degrees of severity of the stem cell deficiency.

Once of the biggest challenges ophthalmologists tell us they are facing is reimbursements. In this issue, we have included a practice management section that takes a look at the challenges many of you are facing just to get paid.

For many ophthalmologists, getting paid is getting more challenging each year. Between the ever-changing reporting requirements from CMS and contractual differences among commercial payers, just keeping up can be a full-time job.

In the field, Insurers are seeking more and more data to document patient outcomes and Medicare has its own reporting requirements through the Merit-based Incentive Payment System (MIPS).

All of this is creating additional headaches for ophthalmologists. We offer a look at some reimbursement trends you may see in the future.

What’s Trending

See what the ophthalmic community is reading on OphthalmologyTimes.com

1 Artificial intelligence in medicine: The good bad, the bad, and the scary
   OphthalmologyTimes.com/Glaucoma360/GoodBadScaryAI

2 Gene therapy offers treatment for X-linked retinitis pigmentosa
   OphthalmologyTimes.com/GeneTherapy/XLRP

3 Estimating the total corneal power key in keratoconus patients
   OphthalmologyTimes.com/Cornea/KeratoconusPatients

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Video

John Berdahl, MD, of Vance Thompson Vision, shares the key highlights from the panel discussion “I have an idea … now what?” featured at the 2020 Glaucoma 360’s New Horizons Forum on “How to translate an idea into breakthrough ideas” in San Francisco.

Go to OphthalmologyTimes.com/Glaucoma360/JohnBerdahl
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- Reduces need for opioids (i.e., fentanyl) during surgery while decreasing VAS pain scores 8
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- Improves uncorrected visual acuity on day after surgery 6
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Li Wenliang: Ophthalmologist hero
Physician was first to sound alarm about coronavirus

MUCH attention these days is focused on the epidemic being caused by a novel coronavirus that originated in Wuhan, China. Apparently, it is quite transmissible and affected persons can transmit the organism to others before any overt signs or symptoms of infection develop.

One infected person, for example, is responsible for starting an outbreak of the disease on a cruise ship. Dozens of passengers contracted the life-threatening infection and 3,500 of them were confined to their rooms on the quarantined ship.

As I write this, the number of persons infected is coming closer to 100,000 and the number of fatalities is approaching 2,000 (many authorities believe these numbers to be substantial underestimates).

A PANDEMIC?
Whether the efforts currently under way to stem the spread of this disease will be effective or a pandemic (epidemic spread involving two or more continents) will ensue remains unknown.

From what I have read, some epidemiologists believe a pandemic is likely, whereas other authorities seem to think the risk is low and are vocally critical of those they accuse of fearmongering. The history of this infection will be written in time as epidemiologists analyze the organism and the response of authorities' interventions.

A sad and interesting part of the story is that played by an ophthalmologist whom many of his fellow Chinese citizens are calling a hero. Li Wenliang is credited with being the first medical professional to sound the alarm on the new virus.

According to news reports, he saw seven patients with a SARS-like infection with conjunctival involvement in his hospital in Wuhan. He sent a message to his medical school classmates to alert them to this observation and urge them to be careful.

When the local authorities became aware of his report, they summoned Dr. Li to a police station, reprimanded him for spreading rumors, threatened him with punishment, and made him sign a form admitting that he was wrong to have sent the message and that he would not repeat the transgression.

Sadly, Dr. Li later developed the infection himself (more than 1,700 medical personnel have so far contracted the disease and six have died).

REPORTS ON SOCIAL MEDIA
Dr. Li sent reports on social media from his hospital bed until the disease took his life. According to news reports, many in China consider him a hero for raising what proved to be a valid concern and a victim of heavy-handed officials.

China’s Supreme Court has vindicated Dr. Li’s actions and criticized the officials who commanded him to be silent. Whether the ultimate outcome of the epidemic would have been different if Dr. Li’s concerns had been taken seriously and more timely public health measures taken is unclear right now (at least to me). But China’s Supreme Court said, “It might have been a fortunate thing ... if the public had listened to [Dr. Li’s] ‘rumor’ at the time.”

It would not have seemed likely to me that a viral epidemic responsible for a life-threatening lung infection would be first recognized by an ophthalmologist.

This fact does point out the role that all physicians can play in being alert to changes in the spectrum of disease in their populations.

REFERENCE
If medications fail, surgery option for treating infectious retinitis

Tools such as OCT can be used to diagnose atrophic retinal detachments

By Lynda Charters; Reviewed by J. Fernando Arevalo, MD, PhD, FACS

Viral retinitis is a rare disease that implies involvement of Herpesviridae, a family of double-stranded DNA viruses characterized by latency within the host’s cells after the primary infection, according to J. Fernando Arevalo, MD, PhD, FACS. Dr. Arevalo is the Edmund F. and Virginia Ball professor of ophthalmology, and chairman of ophthalmology, Johns Hopkins Bayview Medical Center, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore. The viruses implicated include herpes simplex virus (HSV), varicella zoster virus (VZV), herpes zoster viruses, cytomegalovirus (CMV), and perhaps Epstein Barr virus.

The CMV retinitis virus is the most frequently occurring ocular opportunistic infection in patients with AIDS. Before the advent of combination antiretroviral therapy, CMV retinitis developed in 30% of these patients and afterward in less than 1%.

Immunocompetence is the traditional hallmark for retinitis, and their visual needs.”

“The choice of the best surgical option depends on the mechanical factors of the detachment as well as patient factors, such as their immune status, expected survival, control of the retinitis, and their visual needs,” Dr. Arevalo said.

Phacoemulsification and implantation of intraocular lenses are options for treating cataracts that develop and can be performed at the same time the SO is removed.

Immune recovery uveitis can occur in patients with AIDS who develop CMV retinitis. Dr. Arevalo reported that in his series of patients, various pathologies were observed: vitritis, papillitis, macular edema, extensive gliosis, anterior uveitis, cataract, proliferative vitreoretinopathy (PVR) with retinal detachment, and extensive macular edema and an exudative detachment with a macular hole.

‘The choice of the best surgical option depends on [several] factors, such as their immune status, expected survival, control of the retinitis, and their visual needs.’

– J. Fernando Arevalo, MD, PhD, FACS

Patients with AIDS are not the only group in which CMV retinitis can occur. Others include neonates and those in whom immunosuppression was induced, such as after organ transplantation, hematopoietic stem cell transplantation, malignancy, or other causes, Dr. Arevalo noted.

When these patients present, optical coherence tomography can be used to diagnose atrophic retinal detachments resulting from the very thin retinal tissue and exudative retinal detachments in the macula, he advised.

**POLYMERASE CHAIN REACTION**

According to Dr Arevalo, polymerase chain reaction (PCR) can be performed to diagnose the CMV retinitis; while 50- to 100-μl tissue samples are ideal, the disease can be diagnosed with as little as 1 μl of tissue.

Once diagnosed, CMV retinitis can be treated with intravenous ganciclovir (5 mg/kg every 12 hours for two weeks and 5 mg/kg/day for maintenance) or oral valganciclovir (Valcyte, Genentech) (induction dose, 900 mg twice daily for three weeks and 900 mg once daily for maintenance). Intravitreal antiviral drug implants for CMV retinitis include ganciclovir (2.5 mg/0.05-0.1 μl) and foscarnet (Foscavir, Pfizer) (2.4 mg/0.1 μl).

According to Dr. Arevalo, retinal detachments develop in about 20% of this patient population. This detachment rate may decrease with improved therapies.

The number of patients in whom CMV retinitis develops has decreased, which, in turn, decreases the number of retinal detachments.

He noted that the extent and activity of the retinitis are risk factors for detachment. It is imperative to monitor this in patients and prepare a treatment plan.

“With longer patient survival, the need is great for a surgical strategy that will provide the best long-term visual outcome,” he said.

**SILICONE OIL INJECTION**

Vitrectomy with silicone oil (SO) injection and oil removal are the mainstays of therapy for retinal detachment.

Other approaches such as buckle, vitrectomy with gas tamponade, and laser demarcation may also provide excellent visual and anatomic results for retinal detachments, Dr., Arevalo explained.

“The choice of the best surgical option depends on the mechanical factors of the detachment as well as patient factors, such as their immune status, expected survival, control of the retinitis, and their visual needs,” Dr. Arevalo said.

Phacoemulsification and implantation of intraocular lenses are options for treating cataracts that develop and can be performed at the same time the SO is removed.

Immune recovery uveitis can occur in patients with AIDS who develop CMV retinitis. Dr. Arevalo reported that in his series of patients, various pathologies were observed: vitritis, papillitis, macular edema, extensive gliosis, anterior uveitis, cataract, proliferative vitreoretinopathy (PVR) with retinal detachment, and extensive macular edema and an exudative detachment with a macular hole.

**ACUTE RETINAL NECROSIS**

This pathology is the result of HSV-2 in younger adults and HSV-1 or VZV in older adults.

“Immunocompetence is the traditional hallmark of ARN, but recent studies have reported immune dysfunction resulting from medications, malignancy, and other systemic disorders in up to 50% of patients,” Dr. Arevalo explained.

The severe inflammatory reaction that characterizes ARN causes irreversible destruction of retinal and optic nerve tissue. Visual loss in the affected eye and fellow eye can be prevented with anti-inflammatory therapy combined with antiviral treatment.

The initial treatments include the antivirals acyclovir (10 mg/kg/IV three times daily, valacyclovir (2 grams three times daily) for HSV-ARN; and for VZV-ARN 15 mg/kg/IV three times daily and 2 grams four times daily, respectively.

The oral anti-inflammatory prednisolone can be administered for HSV-ARN (30 mg/day) and for VZV-ARN (40-60 mg/day).

The intravitreal antiviral foscarnet can be used to treat HSV-ARN and VZV-ARN (2.4 mg/0.1 milliliter for both).

The topical drugs prednisolone acetate (Pred

Continues on page 10 : Retinitis
INDICATION
DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

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

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

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

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

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

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

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

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

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

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

REFERENCES:

© 2020 Ocular Therapeutix, Inc. All rights reserved.
DEXTENZA is a registered trademark of Ocular Therapeutix, Inc. PP-US-DX-0193
DEXTENZA® (dexamethasone ophthalmic insert) 0.4mg for intracranulcular use

BRIEF SUMMARY: Please see the DEXTENZA Package Insert for full prescribing information for DEXTENZA (06/2019)

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

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

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

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

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

5.4 Fungal Infections
Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate [see Contraindications (4)].

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

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:
- Intracranular Pressure Increase [see Warnings and Precautions (5.1)]
- Bacterial Infection [see Warnings and Precautions (5.2)]
- Viral Infection [see Warnings and Precautions (5.3)]
- Fungal Infection [see Warnings and Precautions (5.4)]
- Delayed Healing [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids include elevated intracranular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation; delayed wound healing; secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera [see Warnings and Precautions (5)].

6.2 Clinical Pharmacology
DEXTENZA was studied in four randomized, vehicle-controlled studies (n = 567). The mean age of the population was 68 years (range 35 to 87 years). 59% were female, and 83% were white. Forty-seven percent had brown iris color and 30% had blue iris color. The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (8%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

5.6 Most Common Non-Ocular Adverse Reactions
The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

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

8.2 Lactation
Systemically administered corticosteroids appear in human milk and could suppress growth and interfere with endogenous corticosteroid production; however the systemic concentration of dexamethasone following administration of DEXTENZA is low [see Clinical Pharmacology (12.3)]. There is no information regarding the presence of dexamethasone in human milk. Women should be informed that breast feeding should be considered along with the mother’s clinical need for DEXTENZA and any potential adverse effects on the breastfed child from DEXTENZA.

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

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

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

MANUFACTURED FOR:
Ocular Therapeutics, Inc.
Bedford, MA 01730 USA
PP-US-DX-0072-V2

DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye including herpes simplex. Use of oral steroids may prolong the course and may exacerbate the severity of many viral infections of the eye including herpes simplex.

RETINITIS
(Continued from page 8)

Forte 1% and cyclopentolate (Cyclo- glycol 0.1%) are administered, respectively, 1 drop four times daily for both HSV-ARN and VZV-ARN and 1 drop twice daily for brachial plexopathies.

Dr. Arevalo noted that he begins with initially higher doses for VZV-ARN and once the PCR results confirm the presence of HSV-ARN, he lowers the doses.

DETACHMENTS OCCUR
Retinal detachments also occur in patients with ARN in 50% to 75% of untreated eyes, within one to two months after the ARN symptoms appear.

Dr. Arevalo also warned that vitreous inflammation can lead to vitreous organization and PVR with a subsequent tractional retinal detachment.

Treatment for ARN could involve a prophylactic vitreous surgery in patients with poor or nonresponsive retinal lesions, especially those near the posterior pole. Dr. Arevalo pointed out that vitreous surgery is indicated for patients with rheumatogenous retinal detachments, a late-stage complication.

“We have had several cases that were resistant to medical therapy but had dramatic improvement of the retinal necrosis lesions immediately after the vitreous surgery, as a result of the removal of the inflammatory cytokines,” he said.

SO TAMPOONADE
Research has found that SO tamponade

has a positive impact on retinal layers thickness and visual acuity in patients who underwent pars plana vitrectomy for rheumatogenous retinal detachment.

SO tamponade is viewed as ideal for retinal detachments, Dr. Arevalo explained, but only for the short term.

Finally, endolaser photoagulation is applied in two or three or more during vitrectomy to normal retinal tissue to surround the posterior border of the necrotic lesions, he explained.

“SO surgery is the preferred surgical approach with oil removal months later during phacoemulsification,” Dr. Arevalo said. “Vitreomcy with gas tamponade, scleral buckle, and laser demarcation follow in that order of preference.”

CONCLUSION
Dr. Arevalo concluded that achieving surgical success requires the permanent closure of retinal holes and relaxation of vitreous traction that might cause new tears.

“Plans para vitrectomy with SO injection obviously accomplishes these objectives; even failed cases with open inferior breaks will have the retinal detachment sufficiently demarcated that the macula remains attached,” he said. “If good adhesion is achieved, oil removal can be considered at a later date in combination with phacoemulsification.”

Ocular Therapeutics

Online Exclusive

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J. FERNANDO AREVALO, MD, PHD, FACS
arevalo@fimm.edu
This article is based on Dr. Arevalo’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Arevalo has no financial interest in any aspect of this report.
Cardiovascular surgery, neurosurgery, orthopedics, and audiology are some of the medical areas that are taking advantage of the technology. However, she emphasized, 3D printing has a huge application in reconstructive surgeries as well as face transplantations.

Within ophthalmology, Dr. Tooley believes that the future may lie in 3D printed corneas, conjunctiva, surgical tools, and glaucoma drainage devices. Science fiction is becoming science fact.

Researchers at Newcastle University, Tyne, UK, have 3D-printed corneas. For every person in the world who receives a cornea transplant, there are 69 others who still need one. As a result, more than 12 million people worldwide have limited sight due to a lack of eye donors.

The research, led by Che Connon, PhD, and Steven Swioklo, PhD, developed the first 3D-printed cornea made with human cells.

Dr. Tooley described a model of a 3D-printed cornea, which can be used to prepare for surgery and create a cutting guide. This guide can be used in the operating room, but they also improve surgical accuracy. Dr. Tooley explained.

Dr. Tooley also noted that 3D printing of surgical guides is especially important for orbital surgeries and craniofacial reconstruction.

The scans of our patients can be custom used to create a 3D model of their anatomy or of the defect to be repaired and that model can be used in the operating room,” she said, describing a model used in a patient with a large orbital medial wall and floor defect resulting from removal of a tumor.

“We were able to have a specific 3D printed guide that exactly matched the defect,” she said. “The titanium implant then could be shaped and modeled according to the 3D printed model, which reduces the time in surgery.”

Finally, customized patient implants are another possibility that can remain inside the patient. These custom implants are used when transplanting a face from the donor to the recipient.

Because this surgery demands absolute precision, cutting guides are printed and placed on the donor to indicate exactly where the cuts are to be made in the bone or tissue. This facilitates a perfect fit on the recipient.

An example of another application was seen in the case of a patient with hemifacial microsomia. The surgeons were able to 3D print a custom implant that matched the normal side of the patient’s face.

“It fit her anatomy and was symmetrical with the other side of her face,” Dr. Tooley said.

The 3D printed materials also can be used in anophthalmic sockets. The printed implants perfectly match the defects in volume and anatomic requirements.

Dr. Tooley concluded that some of the most exciting factors in 3D printing is bioprinting in which live cells are printed onto a live matrix.

“This enables the building of an actual structure, such as ears or parts of the skull. That then can be implanted into patients,” she said. “In ophthalmology, the future is 3D printing of corneas or extra needed tissue. Even more imminent are customized 3D printed glaucoma valves or IOLs. This is a tremendous technology that is at our fingertips.”

Andrea A. Tooley, MD

Mauricio Prieto, MD, shares his experience with the resection of a large retinoblastoma using a 3D printed resection guide. Prieto used the guide in the case of a patient with a large retinoblastoma who was referred to him. The patient was successfully treated and returned to normal vision.

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Physicians on quest to end dysphotopsias in premium IOLs

Demographics driving demand as patients seek spectacle independence

By Alan Aker, MD; Special to Ophthalmology Times

IN THE FACE of continuing reductions in surgeon fees for cataract surgery (averaging $2,800 in 1980 to $560 in 2019), there is interest in procedures not covered by Medicare. These are generally referred to as premium-channel products, and surgeons can bill for these upgrades as private-pay procedures.

With cataract surgery being one of the most commonly performed ophthalmic procedures, one would think that presbyopia-correcting IOLs (premium IOLs) that can provide uncorrected distance and near vision without correction would be widely embraced by both patients and surgeons.

Though presbyopia-correcting IOLs have been available since 2005, the current market penetration of these premium IOLs remains low, however. Patients are accustomed to paying for “upgrades” by both patients and surgeons.

Despite an increased interest among patients for greater freedom from glasses following cataract surgery, patients can be challenging because of issues such as halo, glare, and other visual disturbances known as dysphotopsias. Because of these complaints, currently available premium IOLs are sometimes removed.

This lens exchange or lens replacement surgery is something some surgeons may be uncomfortable performing. In addition, managing these premium IOL patients can be challenging because of additional chair time.

Because of issues such as loss of contrast as well as glare and halos, previously approved technologies have been revisited over the years to reduce patient complaints and to improve utilization of presbyopia-correcting IOLs.

With the availability of the Tecnis Symfony IOL (Johnson & Johnson Vision) to the U.S. market, surgeons were eager to try this new lens, an extended-depth-of-focus lens without the dysphotopsias that may have been seen with other multifocal IOLs.

When we first began implanting the Symfony IOL, eight of our first 100 implants were removed and exchanged because of patient dissatisfaction. These exchanges were performed due to issues relating to either quality of vision or glare and halos.

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Figure 1. Unilateral Uncorrected Distance Visual Acuity 3-6 Months Postoperative

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Figure 2. Unilateral Uncorrected Near Visual Acuity 3-6 Months Postoperative

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Figures 1 and 2 show a comparison of the acuities achieved with both lenses. Note: The model SC9 lens is an investigational device limited to investigational use only and is not available for sale in the United States. (Figures courtesy of Alan Aker, MD)

Patient education about these challenges and careful patient selection has helped to reduce the number of explants we have had to perform. Because of excellent results achieved, we continue to implant the Symfony IOLs, but many patients continue to complain of postoperative issues, such as quality of vision, and especially difficulty driving at night.

SC9 STUDY

We were asked to participate in the ongoing FDA study of the SC9 lens, developed by Stuart Cumming, MD, inventor of the Crystalens (Bausch + Lomb) and founder of CORD (Cumming Ophthalmic Research and Development).

The SC9 is a biconvex optic with a single focal point that affords excellent distance, intermediate, and near vision as a result of its unique design, which consistently places the optic deep in the capsular bag. Our first SC9 was implanted in May 2017, and we are pleased to report that this lens provides our patients with excellent distance, intermediate, and near vision.

Perhaps the most significant aspect of the device is that, in our experience, it provides excellent vision without drawbacks that may be associated with presbyopia-correcting IOLs currently available to our patients in the United States.

Impressed with the results in our study patients, we decided to compare the SC9 in our unmasked study patients with a similar group of Symfony patients.

Our criteria for patient selection for any premium IOL are almost identical to the criteria for inclusion in the SC9 study. Each patient selected for a premium IOL at our cen-
ter has to have the potential for 20/20 vision and no retinal pathology.

Visual acuities are impressive with both lenses, but perhaps the most compelling results have to do with patient satisfaction and the presence or absence of visually disturbing glare and halos.

One patient in this study required an additional surgery to remove his Symfony lens. Despite excellent distance and near vision, the lens was removed because of his inability to drive at night due to glare and halos.

SEEKING FREEDOM FROM GLASSES

With today’s advanced formulas and improved standard lenses, ophthalmologists can correct myopia, hyperopia, and astigmatism. This means it may be possible to greatly reduce the need for glasses for distance for many patients with healthy eyes.

The formulas used to select the lens power for an IOL are excellent. In the absence of retinal or corneal issues, we expect each of our patients to be seeing well enough to drive without glasses following cataract surgery.

THE CHALLENGE AT HAND

Intermediate and near vision without glasses and without halos and glare remains a challenge. By virtue of their design, multifocal and so-called EDOF lenses may put some patients at risk for bothersome glare and halos and dysphotopsias following implantation. Manufacturers have revisited various multifocal designs to reduce issues with night-time glare.

Given a new option to provide excellent acuity at distance, intermediate, and near without having to be concerned with postoperative complaints of loss of contrast, glare, and halos would be a game-changer in terms of utilization.

In addition, such a lens would be welcomed by patients as well as ophthalmic surgeons in the United States and internationally.

DIVING DEEPER

Our mini-study allowed us to compare objective and subjective results of 50 SC9 lenses and 50 Symfony lenses at 3 to 6 months postoperatively in our patients. We have achieved excellent results in both groups, and the quality of vision and the absence of symptoms such as glare and halos in patients with the SC9 is impressive.

Every patient we have implanted with the SC9 has been pleased with the outcome and no patient has complained of significant issues with glare and halos. The SC9 delivers excellent distance, intermediate, and near vision by virtue of the unique design of this new premium IOL.

The longitudinally rigid-lens design consistently places the optic of the SC9 deeper in the eye than other lenses. This was confirmed by Jonathan Soiseth, MS, after an analysis of the depth of SC9 placement in our study patients.

This method of action that places the IOL closer to the nodal point in the eye. Because of this, patients may achieve a dramatic increased depth of focus. This results in excellent distance, intermediate, and near vision without bothersome glare and halos since there are no diffractive or refractive rings on the SC9 optic.

Editor’s Note: The model SC9 lens is an investigational device limited to investigational use only and is not available for sale in the United States.
Researchers targeting risk factors for ectasia after LASIK procedure

Investigators find that percentage of tissue altered can create issues for patients

By Lynda Charters; Reviewed by Marcony R. Santhiago, MD, PhD

**ECTASIA MOST LIKELY** represents a reduction in the mechanical integrity below the threshold required to maintain the corneal shape and curvature, according to Marcony R. Santhiago, MD, PhD, who cited the 21-year-old landmark publication of Theo Seiler, MD, who recommended a residual stromal bed thickness of at least 250 μm (J Refract Surg 1998;14:312-7).

An important caveat in the publication and one that is often forgotten is that the authors emphasized that in order to use the residual stromal bed thickness.

The assumption was that “the biomechanical parameters are constant throughout the corneal thickness,” said Dr. Santhiago, professor of ophthalmology, University of Sao Paulo, Rio de Janeiro, Brazil.

However, he said, that thickness does not remain constant because the corneal tensile strength is not uniform throughout the central cornea, with progressive weakening of the posterior two-thirds of the tissue.

**TRACING THE PERCENT TISSUE ALTERED HIGHWAY**

Considering the recognition of this structural defect, Dr. Santhiago and colleagues proposed a new metric, the percent tissue altered (PTA), that they believe is a more individual metric that takes into account the deficiencies in the biomechanical properties of the corneal tissue.

Dr. Santhiago also proposed a formula. “For LASIK, the metric would be the combination of the flap thickness plus the ablation depth divided by the preoperative central corneal thickness or the thinnest point in the tissue if it is available,” he said.

As early as 2012, Dr. Santhiago and colleagues reported that the PTA was the variable that had the most impact on the changes in the biomechanical parameters after LASIK for myopia performed in normal eyes (J Cataract Refract Surg 2012;38:1222-31 and 2014;40:918-28). These studies showed that PTA increased the role in the weakening of the cornea.

Their next step was to investigate if there was a correlation between a high PTA and the development of ectasia after LASIK. They included eyes in their study that had normal corneal topography and went on to develop ectasia.

“We found that the study group that developed ectasia had significantly higher PTA, but that was not sufficient to establish a relationship,” he said.

They then determined that a PTA value of 40% or greater (with an odds ratio of 223) was a risk factor for ectasia after LASIK (J Cataract Refract Surg 2014;158:87-95). When they investigated the role of PTA in eyes with abnormal topography, the results clearly showed that the more abnormal the Placido disc topography, the lower the PTA values were that were associated with ectasia (J Cataract Refract Surg 2015;31:258-65).

In another investigation (J Cataract Refract Surg 2015;DO1:10.1016/j.jcrs.2015.05.023), Dr. Santhiago and colleagues studied two patient groups that were matched for high PTA; one group developed ectasia and the other did not.

“The group that developed ectasia had significantly thicker flaps,” Dr. Santhiago said. “The same study also had another group with thick flaps and ectasia developed in these eyes only if it was followed by a significant ablation depth with a resultant high PTA. The flap thickness was insufficient to cause ectasia by itself.”

Dr. Santhiago pointed out that in normal eyes, the mean difference between the PTA measured at the central and the thinnest point is 0.2%, considering that in normal eyes the PTA is 26.2% (range, 26.2%-26.4%).

“THe highest difference in our study was only 1.2% (26.2%-27.4%),” he said. “To reach a difference of 2%, a 40-μm difference was needed between the thinnest and central points. Our recommendation is that if that difference is found in the PTA at the central point that it is equal to a value over 2%, perhaps the topography is not as normal as previously considered.”

The effect of the volumes, which is not considered in the PTA, of the flap diameters and thickness also were considered.

Dr. Santhiago and associates studied two theoretical models with varying optical zones and found that a 1% variation in the PTA would facilitate detecting a change in volume as low as 0.3 μm³. A 1-mm variation in the optical zone means a 0.3-mm3 decrease in volume and a 2% variation in PTA. In addition, a 1-mm variation in flap diameter means an increase in the volume of 2.07 mm³.

A recent study (Ophthalmology 2019;126:908-9) validated the original data that a PTA of 40% or higher was the risk factor cut-off point for ectasia. Interestingly, a look-back at the literature on the subject showed numerous reports on ectasia development after LASIK in normal subjects; however, all studies had patients with PTA exceeding 40%, which validates Dr. Santiago’s data. Another validation was seen in a study of surgically induced strain and the associated variables after myopic correction; the study found the PTA to have the strongest correlation with change after refractive surgery.

Based on all of this combined evidence, a high PTA is definitely a risk factor for ectasia after LASIK, Dr. Santhiago concluded.

**TAKE-HOME**

Researchers are looking at issues that can lead to ectasia. The percent tissue altered is a risk factor for ectasia after LASIK.

“We found that the group that developed ectasia had significantly higher PTA, but that was not sufficient to establish a relationship.’

- Marcony R. Santhiago, MD, PhD

Another step in their investigations was to attempt to determine the limits of agreement between the PTA measured at the central and thinnest tissue points.

MARCONY R. SANTHIAGO, MD, PhD

E: marcony.santhiago@hotmail.com

This article is based on Dr. Santhiago’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Santhiago is a consultant for Alcon, Opto, and Zeiss, Zimmer, and a speaker for Abbott, Alcon Optx, Storz Surgical, Zeiss, and Zimmer.
Dry eye disease has become a public health issue, with increasing prevalence in the United States, where more than 16 million people are affected. While dry eye is a common and often chronic problem, particularly in older adults, younger populations are also being affected because of the increasing and constant use of digital devices.

According to Audrey R. Talley Rostov, MD, the increased diagnosis of dry eye disease among younger patients is increasing at an alarming rate, and parents should beware. “We are seeing dry eye disease developing in the pediatric population,” said Dr. Talley Rostov, who is in private practice at Northwest Eye Surgeons, Seattle.

With this in mind, it is more important than ever to establish effective treatments. “The goals of therapeutic intervention are normalization of the tear film, decrease lacrimal gland and ocular surface inflammation, stimulate epithelial healing, and restore the normal neural feedback mechanism to the lacrimal glands,” Dr. Talley Rostov pointed out.

The treatment categories address blepharitis and meibomian gland dysfunction, aqueous deficiency, evaporative goblet cell and mucin deficiency, exposure keratopathy, and co-conspirators. In dysfunctional tear syndrome all of these are not mutually exclusive and there often is overlapping.

WHAT’S NEW IN TREATMENTS?
BLEPHARITIS
Lid hygiene to treat anterior blepharitis is not new, but the addition of hypochlorous solutions used as lid scrubs is and they are beneficial. New topical antiparasitic drugs are available to treat Demodex. The in-office process of mechanical lid debridement has been improved with the introduction of an automated toothbrush-like device. In addition, more attention is being directed to the products used to remove make-up and the choice of cosmetics.

Continues on page 16: Dry eye
Lab tear tests aid reimbursements, clinical application of dry eye
Renewed interest in disease driving research, increasing understanding

By Michael Berg

WHEN A PHYSICIAN seeks to determine a diagnosis and subsequent course of action for a patient, the clinical value of every step in that process is first and foremost. To drive that decision-making process, doctors have relied on laboratory tests about 70% of the time. In every specialty except eye care, that is.

This is no longer the case and eye care specialists are increasingly incorporating point of care in vitro diagnostic, or laboratory testing to aid in their management of patients’ ocular surface health. Renewed interest in dry eye disease has spurred volumes of research and now a greater understanding of the fundamental role of the corneal surface in refractive, cataract and yes, even glaucoma, outcomes.

Eye care specialists also now have algorithms to help guide their use of emerging diagnostic tests and treatment modalities in light of the most up-to-date science and clinical evidence. Several of these algorithms have identified the measurement of laboratory tests, tear osmolarity and matrix metalloproteinases 9 (MMP-9), as key markers of ocular surface health, and have subsequently provided detailed data, discussion and guidance around implementation. For example, the Cornea Clinical Committee of ASCRS has organized these tests.

In the real world, however, the clinical value of a diagnostic test must also be weighed against other practice considerations such as the resources required for its implementation, which are different for laboratory tests versus the standard diagnostics historically utilized by the eye care practitioner.

DETERMINING REIMBURSEMENT
When it comes to insurance reimbursement, a test like TearLab’s osmolarity test is covered according to laboratory rules even though the test sample is not physically sent to an outside lab for analysis. Instead, eye care practitioners perform the test themselves as a CLIA-certified laboratory. Therefore, third-party payers cover and reimburse these tests under the laboratory fee schedule, which for Medicare is the CMS Clinical Laboratory Fee Schedule and for the commercial carriers is found in the provider contract for each specific payer and may vary by provider.

Billing rules and documentation for a lab test are different than what eye care physicians and their staff may be accustomed, requiring additional training, including the clinical staff for proper charting and the billing staff to ensure proper coding and processing.

The tear osmolarity test is universally covered in all 50 states by CMS Medicare, with the caveat that in Florida, there is a local coverage determination which provides an algorithm for testing.

If there are no local or national coverage determinations dictating the use of a test, it diverts to medical necessity rules. These rules are based on the physician’s medical opinion, supported by clinical guidelines, such as the ASCRS Cornea Clinical Committee algorithm, TFOs DEWS II Report and others.

Finally, for CMS Medicare Part B, there is no patient co-pay or deductible, so 100% of the fee is paid to the provider, with no financial impact on the patient.

Continues on page 20: Tear

DRY EYE

(Continued from page 15)

The treatment of posterior blepharitis, topical anti-inflammatory drugs, such as the off-label use of azithromycin, cyclosporine, and lifitegrast (Xiidra, Novartis); microwavable lid masks. Newer technologies such as thermal pulsation and intense pulsed light (IPL) are available, according Dr. Talley Rostov.

MEIBOMIAN GLAND DYSFUNCTION
Thermal pulsation became available in 2011, and the technology has improved because of the introduction of several thermal pulsation devices. The devices are small, handheld, and less expensive. Studies have shown thermal pulsation to be efficacious with increased tear film break-up time and meibomian gland flow.

IPL, a non-laser light source that uses broad-spectrum light, destroys microvasculature and bacteria that introduce the inflammatory mediators to the meibomian glands and liquefies impacted meibomian glands. IPL has proven to be most successful for patients with advanced meibomian gland disease, telangectasias of the lid margins, and rosacea, according to Dr. Talley Rostov.

AQUEOUS DEFICIENCY
The newest approaches to improve lubrication of the ocular surface are ocular inserts and nasal neostimulation, the latter of which involves internal and external electrical stimulation and pharmacologic nasal spray delivery that is in clinical trials.

More artificial tears, some of which are oil-based, have become available; and ocular surface tears can be preserved with the reintroduction of scleral lenses.

The real goal is treating the underlying inflammatory disease, which can be accomplished by using steroids, cyclosporine A, lifitegrast, autologous serum tears, amniotic membrane both cryopreserved and frozen, and omega 3.

EVAPORATIVE GOBLET CELL AND MUCIN DEFICIENCY
With the goal of replenishing goblet cells, cyclosporine A is useful based on phase III studies, lifitegrast based on its anti-inflammatory effects, and compounded vitamin A ointment are the key innovations. Scleral lenses are also useful.

EXPOSURE KERATOPATHY
Moist chamber goggles are an innovation in this area. However, patients also should take advantage of the tried-and-true treatments such as lubricating gel, lid tape, lid surgery, gold eyelid weights, and tarsorraphy.

A number of overlapping factors can be at work in dysfunctional tear syndrome that can exacerbate or maskquerade as dry eye tear syndrome. These include superior limbic keratoconjunctivitis, topical medication toxicity, superficial punctate keratitis, mucous fishering syndrome, contact lens-related toxicity, chemical toxicity, allergic and atopic conjunctivitis, conjunctivochalasis, and floppy lid syndrome.

New anti-parasitic drugs are being investigated to treat Demodex, but are not yet approved.
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ENDOPHTHALMITIS

(Continued from page 1)

permeability, decreased toxicity, and slower degradation rates.

Dr. Behlau and her colleague Joseph Ciolino, MD, explored an antibacterial-eluting contact lens that contained ciprofloxacin in one model and econazole in another model, both of which are small-molecule drugs.

The ciprofloxacin-containing contact lens was a zero-order delivery system, and the econazole-containing lens demonstrated efficacy in the delivery of that anti-fungal drug.

One drawback to this is that producing such a treatment modality is burdensome and the question regarding how efficiently the drugs hit their targets remains unanswered, she explained.

A mucoadhesive contact lens, developed by Prashad Garg, MD, was formulated from polyethylene glycol, glycerol, chitosan, and glacial acetic acid that contains moxifloxacin 0.4% and dexamethasone 0.1%. With a small burst, this contact lens achieved zero-order kinetics.

A rabbit keratitis study showed that the moxifloxacin concentrations to the lens and cornea were high, but those in the aqueous and vitreous were wanting.

“This result supports the notion that topical antibiotics do not work because they cannot penetrate to where they need to be,” Dr. Behlau said.

“The concept of using them is not beneficial. The contact lenses provide better penetration, but the complexity and cost increase and the small molecules are limited.”

Other approaches—including subconjunctivally, intracameral, and transsclerally—are reliably unreliable, she noted.

SYSTEMIC DELIVERY

In light of these short falls, all roads lead back to systemic administration, Dr. Behlau said, but this comes with disadvantages.

Providing access to drugs through the retinal pigment epithelium is confounded by the efflux pumps, P-glycans, and the multidrug resistant associated proteins, Dr. Behlau explained. The back of the eye is inaccessible to systemically administered drugs.

The rule of thumb is that if the data show that a new drug can penetrate into the central nervous system, the drug often can penetrate into the eye. However, in order to access the eye, higher doses are needed and often intravenous administration, she noted.

The fluoroquinolones and linezolid can reach the eye when administered systemically, the latter of which may be useful for methicillin-resistant Staphylococcus aureus. Systemically administered antifungals are also useful for penetrating the eye.

INTRAVITREAL ACCESS

Issues with this route of delivery are the sizes of the molecules injected and the elimination times. The route of elimination—anteriorly or posteriorly—affects the ocular retention time, with drugs eliminated anteriorly are retained longer.

“The fluoroquinolones, for example, clear the eye posteriorly, which is why the drug has to be administered so frequently,” Dr. Behlau noted.

It is also noteworthy that inflammation and pars plana vitrectomy increase the rate of elimination. For example, ciprofloxacin injected intravitreally remains in the eye for about 60 hours in an uninfected eye. In the presence of an infection, the drug is eliminated in about 16 hours.

DRUG-DEVICE COMBINATIONS

There has been an explosion in the use of these drug-delivery system, as evidenced by the drug-eluting contact lenses and intracameral implants, and in devices to treat age-related macular degeneration and diabetic retinopathy with direct delivery into the posterior segment, she explained.

According to Dr. Behlau, drug-device combinations in many cases overcome the ocular barriers and elimination mechanisms.

“Anterior segment systems enhance the precorneal retention and tissue permeation,” she explained.

“Posterior segment devices require sustained drug release to minimize the injection frequency.”

Dr. Behlau pointed out that these devices are invasive and importantly carry the risk of foreign body infection.

An antimicrobial device implant is the first of its kind that can overcome some shortcomings of these drug devices is the antimicrobial silk ocular drug-delivery implant that was designed by Dr. Behlau, Chiara Ghezzi, PhD, and David Kaplan, PhD, Biomedical Engineering at Tufts University, Boston, for treating chronic posterior segment diseases.

This implant is coated with N,N-hexy, methyl polyethyleneimine to prevent infection, be bio-compatible, and can enable the zero-order sustained delivery of larger molecules, Dr. Behlau explained.

This 4- to 5-mm device, with an inner diameter than can accommodate a 27-gauge needle, can be implanted without creating an incision. It also can retain in the eye in the pars plana as a result of its peanut shape. This device can stay in the eye for eight months without the need for an antibiotic.

“My hope is that this type of implant can be used to treat endophthalmitis over a long period of time and other diseases,” Dr. Behlau concluded.

“This device has versatility and plasticity, it is programmable for individualized drug delivery and it is 100% biodegradable.”
INDICATIONS AND USAGE
FLAREX® (fluorometholone acetate ophthalmic suspension) is indicated for use in the treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
Contraindicated in acute superficial herpes simplex keratitis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; mycobacterial infection of the eye; fungal diseases; acute purulent untreated infections, which like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; and in those persons who have known hypersensitivity to any component of this preparation. Please see brief summary of Full Prescribing Information on the adjacent page.

STUDY DESIGN:
The efficacy and safety of FLAREX (n=41) vs FML* (n=37) were evaluated in a randomized, double-blind clinical trial in 78 patients with ocular surface inflammation (eg, conjunctivitis, episcleritis, scleritis) in one or both eyes. In a separate randomized, double-blind clinical trial in 82 patients with ocular surface inflammation in one or both eyes, the efficacy and safety of FLAREX (n=37) vs prednisolone acetate 1.0% (n=45) were evaluated. In these studies, patients administered either FLAREX or FML*/prednisolone acetate 1.0% every 2 hours for the first 2 days and then every 4 hours thereafter, with signs and symptoms of inflammation assessed at Days 1, 3, 8, and 13. At each visit, investigators determined if symptoms in the involved eye were resolved (cured), improved, unchanged, or worsened. If a patient was rated as cured before the end of the study, steroid drops were discontinued and the patient was considered to have completed the trial.2

Cost information based on Wholesale Acquisition Cost (WAC), 2019 data.

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When a practitioner uses his or her medical judgment along with the established guidelines to determine when to perform a tear osmolarity test, the decision must be properly documented in the patient's chart. Because the documentation for laboratory testing differs from routine procedures and services, extra care should be taken to ensure four simple items are always included:

1. A sign or symptom of disease must be present and identified during the patient's current visit, or if the patient is being managed from a prior diagnosis, the condition must be unstable.

2. The test must be ordered and although the order may be verbal, that order must be indicated in the chart.

3. The test result - and if those results are normal or abnormal - must be noted.

4. The test results must appear in the patient management plan at the end of the visit, even if the test is normal. In laboratory parlance, normal tests are considered "rule-out" tests, and if they were ordered due to a symptom indicating the possibility of a disease, the normal test ruling out that disease is fully reimbursable.

Even if the test is normal and it doesn’t correlate with the final diagnosis, its test result must be included in the patient management plan indicating that the disease was ruled out. If it’s not in the plan, payers assume that the test was not used to manage the patient and they will not pay for it.

When these criteria are documented in the chart appropriately, the test will meet the medical necessity rules, ensuring reimbursement. Additionally, such documentation helps to ensure the practice survives any potential audits.

The ASCRS algorithm recommends surgeons evaluate all patients in the preoperative setting for OSD by performing both osmolarity and MMP-9 testing even if they do not have a sign or symptom of disease. Only in cases where a sign or symptom for OSD does not exist, osmolarity and MMP-9 would be considered a screening test and not a reimbursed test. Practices then must decide if they want to charge patients or bundle the cost of the test with a premium IOL package, for example. For cataract surgery, due to the high prevalence of OSD symptoms in the elderly, it is rare that a sign or symptom of OSD is not identified.

CONCLUSION

With supporting evidence like the ASCRS OSD algorithm, eye care providers have further incentive to implement osmolarity and MMP-9 testing as the evolving standard of care. Whether used to confirm or rule-out a diagnosis, the eye care practitioner now, for the first time, has available to it in vitro laboratory testing to aid in the diagnosis and management of disease, just like other specialties utilize in 70% of their health care decisions. When a sign or symptom of disease is present and appropriate documentation is provided, the test is eligible for third-party reimbursement.
Care delivery: Motivating patients with mobile devices

New tools helping ophthalmologists enhance care offered in their practice

By Lynda Charters; Reviewed by Leslie S. Jones, MD

Ophthalmology is poised for seismic shifts sparked by advances in technologically advanced medical devices that are driving changes in patient care and impacting the lives of patients.

The delivery of patient care is moving into the forefront, with the focus shifting increasingly more from office-based services to mobile devices to further enhance delivery of care.

According to Leslie S. Jones, MD, associate professor and chair of ophthalmology, Howard University, Washington, DC, a revolution is ongoing.

“There are thousands of mobile apps with which patients can interface,” she said. “Google Play and Apple have developed many apps to help us care for our patients. These apps have become important elements in contemporary digital mobile use.”

Some apps in particular are outstanding aids for patients. EyeDropAlarm is one such product that provides an easy reminder when drops are due to be instilled. Medisafe Medication Management also provides drop, pill, and medicine reminders; this app also provides for friends and family members to be keyed in as a double check that the medications will be taken at the appropriate time.

GoodRx-Save on Prescriptions provide discount coupons for medications that can shave up to 80% off of the pharmacy bill instantly. This app also can be used to locate the best prices at area pharmacies.

An app called Pocket Pharmacist provides important information about potential drug interactions.

More and more artificial intelligence (AI) apps are popping up. One that Dr. Jones recommends for her patients is Seeing AI, a talking camera for blind patients. The individual can use his or her smartphone to scan the environment. The smartphone then interprets images and feeds back oral information to a visually challenged individual.

Dr. Jones described Be My Eyes-Helping the Blind as “excellent.” This app works by linking blind individuals with sighted volunteers for help with various tasks. Dr. Jones serves as a volunteer for this app.

Self-testing devices also are part of this revolution in mobile care delivery, and an app titled Macula-Tester is one of them. Using this app, patients can test their vision and send the information to their doctor’s office.

“This is a very good app for patients with dry age-related macular degeneration [AMD] that they can use to test themselves at home,” she said. “This app can detect a scotoma or metamorphopsia.”

Dr. Jones keeps iPads in the office to obtain consent for various procedures, which are shown in schematic form.

“These devices have excellent contrast sensitivity and provide white writing on a black background for increased contrast,” she explained. “Type magnification is also a feature, as are the availability of voice commands as well as voice over and talk back features that are available on the devices.”

For patients who may not be familiar with these features, she sends them for low-vision consultation or for help provided by technicians in her office.

“Patients often do not know that they already own a device that can be helpful to them,” Dr. Jones said.

A device called iCare Home allows patients to monitor their IOP at home. Using this device, they can obtain data about diurnal fluctuations in IOP at all times during the day. Patients with glaucoma have much more pronounced IOP fluctuations, making it particularly important that the values are tracked during the day.

“Even if the IOPs are measured in the office from 7 a.m. to 9 p.m., the peak IOP may not be captured during that window,” Dr. Jones noted. “The peak IOP may be an independent risk factor for worsening of glaucoma.”

Dr. Jones rents the instrument to patients for a small fee for a few days so that she can better determine her patients’ IOP fluctuations and inform her decision-making about care.

A small device, ForeseeHome, facilitates monitoring of dry AMD at home. The device, which is covered by Medicare for eligible patients with 20/60 vision, can detect small changes associated with dry AMD earlier with daily monitoring without undergoing dilation.

According to Dr. Jones, the machine monitors the patient for any changes and when they occur the device alerts the doctor.

“Mobile at-home monitoring devices have many advantages in that they reduce the burden of frequent office visits, provide additional information for medical decision-making and customization of care,” she said.

On the flip side, the cost of the device, maintenance, and patient compliance are involved.

Dr. Jones pointed out that patient portals are the most useful thing in her practice to engage patients. Through these portals, patients can access their medical data, schedule appointments and appointment reminders, request medication refills and medication reminders, and have access to secure messaging for interactions with technicians and doctors.

A study of 164,477 patients observed using patient portals during a one-year period showed that connections to health resources via various devices resulted in higher rates of outpatient visits, fewer trips to the emergency room, and fewer preventable hospital stays (Read et al. Plos One 2019;14(6):e0217636).

Dr. Jones summarized that in order to engage patients with the use of mobile devices in clinics, physicians can recommend apps that they have downloaded and tested.

“The apps can serve as medication reminders, to provide pharmacy benefits, to identify medication interactions, and for self-monitoring,” she concluded. “Home monitoring devices of IOP and macular status also can be considered for use in practices. I always recommend that my patients use my practice’s patient portal, even to send me messages. It provides a more direct way for me to contact them.”

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

LESLIE S. JONES, MD
E: l_s_jones@howard.edu
Dr. Jones has no financial interest in any aspect of this report.
The first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis\textsuperscript{1-3}

**Indication**

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

**Important Safety Information**

**WARNINGS AND PRECAUTIONS**

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

**ADVERSE REACTIONS**

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

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

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*Cenegermin-bkbj, the active ingredient in OXERVATE, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues\textsuperscript{5}*

*NGF is an endogenous protein involved in the differentiation and maintenance of neurons, and acts through specific high-affinity (ie, TrkA) and low-affinity (ie, p75NTR) NGF receptors in the anterior segment of the eye to support corneal innervation and integrity.\textsuperscript{1} Endogenous NGF is believed to support corneal integrity through 3 primary mechanisms (shown in preclinical models): corneal innervation, reflex tear secretion, and corneal epithelial cell proliferation and differentiation\textsuperscript{3,6,7}*

**Explore the breakthrough therapy at Oxervate.com/HCP**

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**References:**

1. OXERVATE (cenegermin-bkbj) full prescribing information. Dompé. October 2019.
Brief Summary of Safety
Consult the full Prescribing Information for complete product information.

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

DOSE AND ADMINISTRATION
Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration. If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

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

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks. Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data
In embroyfetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species.

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

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

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).
Neurotrophic keratopathy: Diagnostics, treatment merge

New breakthroughs restore corneal sensation, vision in patients

By Lynda Charters; Reviewed by Francisco C. Figueiredo, MD, PhD, FRCOphth

Impairment or total absence of corneal sensation are the hallmarks of this degenerative disease, and depending on its severity, the clinical manifestations can range from punctate epitheliopathy persistent epithelial defects to corneal perforation.

A specific therapeutic approach is required to address the disease presentation, which is described by Mackie’s classification of three stages of severity. The clinical presentation is always the same regardless of the etiology, according to Francisco C. Figueiredo, MD, PhD, FRCOphth, professor of ophthalmology, Department of Ophthalmology, Newcastle University, Newcastle-upon-Tyne, UK.

Stage I is characterized by epithelial hyperplasia and irregularity, haze, punctate keratopathy, superficial vascularization, and stromal scarring; stage II by a superior epithelial defect usually in the superior quadrant, with smooth and rolled edges of the defect, and stromal edema; and stage III corneal ulceration, stromal melting, and even perforation.

Slit-lamp examinations show findings similar to dry eye disease, including decreased tear film breakup time, superficial punctate keratitis, and decreased blinking. The clinical picture may progress to slow healing of the epithelial defect with smooth and rolled edges with or without stromal involvement.

A diagnosis can be established by testing of the corneal sensation using corneal esthesiometry in the central and peripheral parts of the cornea. Touching the cornea with a cotton swab is a qualitative test of sensation.

The most widely used test is the Cochet-Bonnet direct contact test. In vivo confocal microscopy can provide quantitative and qualitative assessment of the corneal nerves and can show mild to total damage of the corneal nerves. A neurologic examination can provide a full assessment of the cranial nerves.

Management requires grading of the disease stage and an array of medical and surgical interventions. With stage I disease, Dr. Figueiredo advised, reviewing use of all the topical treatments, and discontinuing most of them, particularly the ones with preservatives because of potential toxicities that can worsen the corneal surface.

“This may be combined with ‘unpreserved lubricants, including artificial tears and ointments, and punctal plugs,’” he said.

In stage II disease, Dr. Figueiredo recommends the same approach as in stage I with the addition of prophylactic topical antibiotics; eyelid closure that includes tarsorrhaphy, taping, pads, or botulinum toxin; bandage contact lens; serum eye drops, including autologous/allogeneic; and amniotic membrane transplant in some cases.

Stage III disease requires all the factors in stages I and II plus topical matrix metalloproteinase inhibitors to prevent collagen layer breakdown, tissue adhesives plus amniotic membrane plus bandage contact lens for small perforations, and surgery such as corneal gluing, tectonic lamellar or penetrating keratoplasty for larger perforations.

The newest treatments include the use of ReGeneraTing Agent, which facilitates reconstruction of the extracellular matrix that will help tissue repair and regeneration. Cacicol (Thea Labs), a new matrix therapy to promote corneal healing, is currently in a clinical trial but the results are as yet unpublished; recombinant human nerve growth factor (rhNGF), a topical therapy applied six times daily for eight weeks, is being used rather successfully in moderate to severe neurotrophic keratopathy that has been refractory to surgical treatment; the product was approved recently in the US and is available under the name cenegermin (Oxervate, Dompe); and, direct corneal neurotization involves transplanting contralateral supraorbital and supratrochlear branches of the ophthalmic division of the trigeminal nerve, indirect neurotization involves using sural nerve transplant in some cases that connects the contralateral branches of the ophthalmic division of the trigeminal nerve.

According to Dr. Figueiredo, rhNGF is promising and has shown extremely good results.

“Neurotrophic keratopathy is a chronic, serious potentially blinding and refractory corneal degenerative disease that often poses significant treatment challenges, especially when complicated by other concurrent ocular comorbidities, such as exposure keratopathy, dry eyes, and limbal stem cell deficiency,” he concluded. “New treatments, such as rhNGF, neurotization, and matrix therapy have completely changed our current treatment protocol.”

TAKE-HOME

› Neurotrophic keratopathy is a challenging and potentially blinding disease that is responding to recombinant human nerve growth factor, corneal neurotization and matrix therapy agents to restore corneal sensation and visual acuity.

‘New treatments, such as rhNGF, neurotization, and matrix therapy have completely changed our current treatment protocol.’

- Francisco C. Figueiredo, MD, PhD, FRCOphth

The causes of the disease are highly variable and range from genetic, ocular, neurological, and systemic, with herpes virus, post-surgical trigeminal nerve damage, chemical burns, and diabetes causing the preponderance of the cases, according to Dr. Figueiredo.

DIAGNOSIS AND MANAGEMENT

Patients present with nonspecific complaints, such as dryness, discomfort, photophobia, decreased vision, and worse symptoms upon awakening that are aggravated by environmental factors such as air conditioning and personal computers.

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Hardware, software offer surgeons a window to cornea diagnosis

Topographers/tomographers cornerstone for evaluations

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

ADVANCES IN HARDWARE and software make corneal topography and tomography useful tools for corneal risk assessment 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.

“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, professor of ophthalmology, University of Pittsburgh, Pittsburgh. “Hopefully, these processes will be improved in the future through a combination of biomechanical factors, topographic indices, and surgery-induced risk stratification.”

DEVICES 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.

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.

In post-LASIK ectasia, the cornea starts to bulge forwards at a variable time after LASIK, PRK, or SMILE corneal laser eye surgery, much like keratoconus.

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 (eg., 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.”

LASIK involves removing corneal tissue and reshaping the corneal wall. This procedure is effective for correcting issues such as nearsightedness, farsightedness, and astigmatism, but it also inherently results in a thinner cornea.

THE RELIABILITY OF THESE SCORES DEPENDS ON THE RELIABILITY OF THE INDIVIDUAL FACTORS THAT ARE USED TO CALCULATE THEM.

– Vishal Jhanji, MD

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, which also imaged the posterior cornea.

Dr. Jhanji pointed out that with information about posterior surface elevation, keratoconus began to be diagnosed more efficiently. Keratoconus affects 86 in 100,000 people, resulting in visual loss due to increasing irregular corneal astigmatism, and the quality of life declines in patients. Ophthalmologists can stabilize the disease or improve vision by utilizing corneal cross-linking (CXL) and grafting, but these carry risks.

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.

LIMITATIONS OF DEVICE-BASED SCREENING

Dr. Jhanji pointed out that 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 could be interpreted as providing a clear indication of ectasia development and progression, there are other factors which must 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.

CONCLUSION

“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.”

VISHAL JHANJI, MD

This article is based on a presentation by Dr. Jhanji at the American Academy of Ophthalmology annual meeting. He has no relevant financial interests to disclose.
Smartphones, tablets stepping up as diagnostic technology options

Portable devices can diagnose glaucoma, evaluate optic nerve

By Lynda Charters

NEW TECHNOLOGY IS good if it does what it purports to do and sometimes goes beyond that.

Both smartphone-based fundus photography and tablet-based visual field testing with fundus photography and Humphrey visual field testing seem to deliver for evaluating the optic nerve and diagnosing glaucoma.

These results are important, and ultimately could give ophthalmologists another diagnostic tool to better serve patients.

In the Philippines, where Patricia Anne Santos Tecson, MD, MBA, is a resident at The Medical City, Pasig City, glaucoma is the third-leading cause of bilateral blindness and the fifth-leading cause of low vision.

The Philippines is a nation that includes more than 7,600 islands. Because of geographic complications, many patients do not have ready access to ophthalmologists, of which there are only 1,800.

“Major challenge in this setting are accessibility and affordability, particularly in rural and remote areas that do not have eye centers and doctors and specialists available for consultation,” Dr. Tecson said. “This scenario makes diagnosis hard if not impossible and many cases of glaucoma are undetected.”

The accessibility issue has been eased in recent years by the advent of teleophthalmology and the increasing growth of internet use, which has resulted in more documentation of fundus photos and assessment of visual field defects remotely.

Affordability remains an issue because of the higher costs of advanced technology, such as the Visucam 500 and the Humphrey Field Analyzer (HFA) II-I (both from Carl Zeiss Meditec), respectively, she noted.

Perhaps one remedy to this challenge is the usage of less-expensive portable devices, such as the iPhone 6s+ (Apple) with a Volk 20-D lens and the iPad3 (Apple) with an Melbourne Rapid Fields (MRF) testing application, she suggested.

THE STUDY

To determine if these alternative technologies stack up against standard fundus photographs and visual field tests, Dr. Tecson and colleagues evaluated the iPad 3 with MRF and an iPhone 6s+ that took mydriatic fundus photographs with a 20-D lens.

This prospective, cross-sectional, single-center study included 96 eyes of 51 patients; 47 eyes were nonglaucomatous and 49 eyes were glaucomatous and had been diagnosed previously by a glaucoma specialist.

All patients completed two visits. At the first visit, the patients provided a history and underwent a dilated ocular examination; two fundus photographs were taken using the Visucam 500 and the iPhone 6s+. At the second visit, the visual fields were tested using the Zeiss HFA II-I and the 24-2 threshold SITA test and the iPad 3 with a MRF full grid.

Dr. Tecson noted that the fundus photographs and visual field tests were masked; the clinicians could see only the corresponding study identification numbers.

Two independent masked glaucoma specialists were not told which devices were used for the fundus photographs and visual field tests, and they had no information from the history or ocular examination. A third glaucoma specialist assisted when there was disagreement between the two readers.

The primary outcomes measure was the validity of the devices for accurately diagnosing glaucoma based on the Visucam and iPhone photo and the MRF and HFA tests.

The secondary outcomes were the accuracy of identification of the parameters in the fundus photos, the agreement between the Visucam and iPhone photos for each parameter, and the inter-rater agreement between the standard agreement between standard and portable devices.

“Compared to the Visucam instrument, 19 photos obtained using the iPhone had poor image quality, seven of which were considered ungradable and reduced the number of study eyes to 89,” Dr. Tecson said.

Frequency table analysis showed that the accuracy of both portable devices based on the parameters assessed were good. The iPhone had a sensitivity of 100%, but, she pointed out, that this was noted to be overreported due to the seven eyes that were excluded from analysis; the iPhone specificity was 89.36%, the positive predictive value 89.36%, and the negative predictive value 100%. The MRF had respective values of 81.82%, 86.54%, 83.72%, and 84.91%.

Among the 10 glaucoma parameters tested, the ones that were most accurate were those most consistently identified with the readings and their standard counterparts, she said. These included rim pallor, overpass cupping, and peripapillary atrophy. The least accurate were the lamina cribrosa visibility, barring of vessels, and nerve fiber layer defect.

The studied parameters also were assessed in the standard Visucam photos, and the most sensitive parameter was bayoneting of the vessels. Regarding the vertical cup-to-disc ratio, a good correlation of 0.89 was found between the Visucam and iPhone by Pearson’s correlation.

The readers were likely to have more discrepancies when grading the vertical cup-to-disc ratio on the iPhone compared with the Visucam, Dr. Tecson noted, such as 0.82 versus 0.96. The absolute difference indicated that between the two methods, 99% of eyes (86 of 89 eyes) differed by 0.2 or less.

The mean vertical cup-to-disc ratio in normal eyes with the Visucam was 0.52 and with the iPhone 6s+ 0.56, indicating the possibility that the glaucoma prevalence can be overestimated.

The inter-instrument agreement was good for all parameters studied, with all kappa values over 0.61 for the Humphrey field analysis.

Dr. Tecson concluded that smartphone-based fundus photography and tablet-based visual field testing are comparable to standard photographs and visual field testing in evaluating the optic nerve and diagnosing patients with glaucoma.

“These portable devices can be reliable and appropriate for diagnosing glaucoma and facilitating documentation and testing in remote areas and in a wider range of settings,” she said, recommending that a larger study be performed and that fundus photos be compared with stereoscopic optic disc photos.

PATRICIA ANNE SANTOS TECSON, MBA, MD

p: 632/988-7000

This article is based on Dr. Santos Tecson’s presentation at the American Academy of Ophthalmology’s annual meeting. She has no financial disclosures to report.
INDICATIONS AND USAGE
CEQUA™ (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

REFERENCES:
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ADVERSE REACTIONS
The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

Use with Contact Lenses: CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

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

References:
Brief Summary of Prescribing Information for CEQUA™ (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use
CEQUA™ (cyclosporine ophthalmic solution) 0.09%
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE
CEQUA ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

CONTRAINDICATIONS
None.

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CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reininserted 15 minutes following administration of CEQUA ophthalmic solution.

ADVERSE REACTIONS
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.

In clinical trials, 769 patients received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated patients were female (83%).

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no adequate and well-controlled studies of CEQUA administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses.

Data
Animal Data
Oral administration of cyclosporine oral solution (USP) to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight, and skeletal retardations. These doses (normalized to body weight) were approximately 3200 and 21,000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 mcg/kg/day, respectively. No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 1800 and 6400 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 4800 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (approximately 1600 times greater than the MRHOD).

Lactation
Risk Summary
Cyclosporine blood concentrations are low following topical ocular administration of CEQUA. There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on breastfed infants and milk production. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CEQUA and any potential adverse effects on the breastfed child from cyclosporine.

Pediatric Use
The safety and efficacy of CEQUA ophthalmic solution have not been established in pediatric patients below the age of 18.

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

PATIENT COUNSELING INFORMATION
Handling the Vial
Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the solution. Advise patients also not to touch the vial tip to their eye to avoid the potential for injury to the eye.

Use with Contact Lenses
CEQUA should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the solution. Lenses may be reininserted 15 minutes following administration of CEQUA ophthalmic solution.

Administration
Advise patients that the solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

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OCT key tool in determining glaucoma progression

Study demonstrates value as an adjunct for visual fields

By Cheryl Guttman Krader, BS, Pharm; Reviewed by Felipe A. Medeiros, MD, PhD

Glaucoma worsens slowly in most patients who are affected with the disease, but a substantial number of patients with glaucoma show at least moderate progression over time based on monitoring with optical coherence tomography (OCT) and visual fields.

Although OCT can detect progression in patients across all stages of disease, the findings from OCT and standard automated perimetry (SAP) frequently disagree.

Therefore, it is essential that patients who have been diagnosed with glaucoma be followed for progression using both modalities, according to Felipe A. Medeiros, MD, PhD, Distinguished Professor of Ophthalmology, and Joseph A.C. Wadsworth Endowed Chairman, Duke University School of Medicine, Durham, NC.

The above information and recommendations made by Dr. Medeiros are based on findings from analyses of data collected in the Duke Glaucoma Registry Study from over 27,000 eyes of over 14,000 patients with glaucoma or who were glaucoma suspects.

‘Visual field testing remains the primary method of assessing glaucoma progression. The findings of our study are helpful for understanding where OCT is useful.’

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OCT imaging in this patient showed a decrease in RNFL thickness superiorly over time, but it was attributable to a region of vitreous traction that was pulling on the RNFL, and the change disappeared after the traction was released.

Dr. Medeiros also noted that different OCT instruments evaluate progression differently, but it is always essential to consider whether change is glaucoma-related.

"The Guided Progression Analysis software for a Zeiss OCT platform reports the statistical significance of an event analysis over time, but that feature does not decrease the importance of looking at the scans over time and making sure the quality is adequate," he concluded.

However, the software users will have to do some work to determine some final data.

"The software for Spectralis (Heidelberg Engineering) does not give the statistical significance of the change, and so users of that device need to determine the clinical significance themselves," Dr. Medeiros explained.

TAKE-HOME

◗ Structural evaluation with OCT and functional testing with visual fields should be used throughout the glaucoma disease continuum to detect progression.

CONCLUSION

"We believe our undertaking is probably the largest analysis of longitudinal SD OCT and SAP results to date," Dr. Medeiros said. "Visual field testing remains the primary method of assessing glaucomatous progression. The findings of our study are helpful for understanding where OCT is useful."

In analyzing the data, eyes were categorized as having slow, moderate, fast, or catastrophic change over time based on average annual change in SAP or average retinal nerve fiber layer (RNFL) thickness change criteria. For example, eyes with <0.5 dB/year change in SAP or <1 μm/year loss of average RNFL were classified as experiencing slow change.

Dr. Medeiros explained that the cut-off of <1 μm/year was chosen to define slow change based on findings of a study that looked at the impact of normal aging on change in RNFL thickness.

Data from healthy subjects showed that the 95% confidence interval for age-related loss was up to 1 μm/year.

“Therefore, a slope of RNFL thickness change that is >1 μm/year is likely glaucoma progression,” he said.

The results from analyzing the data in the Duke Glaucoma Registry showed that approximately 30% of eyes experienced moderate or faster glaucomatous progression over time.

When the subjects were grouped according to glaucoma severity, it was found that in the group with early glaucoma at baseline, SD OCT detected many more eyes that were progressing fast than did visual fields.

Among subjects who had severe glaucoma at baseline, the proportion identified as having fast or catastrophic progression was approximately the same using SD OCT and visual fields. The eyes identified by the two tests, however, were not the same.

“We found that most eyes identified as having fast or catastrophic progression by OCT would have been classified as showing slow or moderate progression by their visual fields and vice versa,” Dr. Medeiros said. “This result drives our conclusion that both structural and functional tests should be used throughout the disease continuum to monitor for progression in patients with glaucoma.”

Although changes noted on serial OCT scans may indicate disease progression, clinicians need to consider whether the change is the result of worsening glaucoma or has some other cause.

A case of a patient with vitreous traction illustrates this point. The OCT imaging in this patient showed a decrease in RNFL thickness superiorly over time, but it was attributable to a region of vitreous traction that was pulling on the RNFL, and the change disappeared after the traction was released.

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TAKE-HOME

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CONCLUSION

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The interest in gene therapy is increasing exponentially as evidenced by the more than 1,100 gene therapy protocols that the FDA has approved since 2012. With these trials come concerns about the complications and the costs associated with gene and cell-based therapies. David J. Wilson, MD, discussed the factors that might not necessarily be readily apparent to clinicians. He also urged ophthalmologists to gain a real understanding of how trials are conducted, that is, complications are not necessarily reported and complications do occur that can affect patients down the line.

Dr. Wilson is director and professor, Casey Eye Institute, Oregon Health and Science University, Portland. A great deal of oversight is involved in gene therapy trials that includes the FDA, Office of Biotechnology Activities, Recombinant DNA Advisory Committee, and the Genetic Modification Clinical Research Information System, but complications generally are not discussed at professional meetings, Dr. Wilson said.

Complications, costs of gene and cell-based therapy targeted

In search of options, researchers find two areas in need of further study

By Lynda Charters; Reviewed by David J. Wilson, MD

The interest in gene therapy is increasing exponentially as evidenced by the more than 1,100 gene therapy protocols that the FDA has approved since 2012. With these trials come concerns about the complications and the costs associated with gene and cell-based therapies. David J. Wilson, MD, discussed the factors that might not necessarily be readily apparent to clinicians. He also urged ophthalmologists to gain a real understanding of how trials are conducted, that is, complications are not necessarily reported and complications do occur that can affect patients down the line.

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**Complications in Gene and Cell Therapies**

“Immune response and wound healing will definitely be factors with gene and cell-based therapies,” Dr. Wilson said.

These agents under development differ from pharmacologic agents, Dr. Wilson explained, adding that much more goes into the presurgical manufacturing and development of gene and cell therapies and there are typical surgical considerations for injections, including position, fluid, material, injection rate, and catheter size.

The next consideration is the immune response and the idea that there is complete immune privilege in the retina is not accurate; it does have a definite immune response. Wound healing is another factor, although that does not differ substantially from other indications for vitreoretinal surgery in the mechanical issues and cell reaction. He described some potential issues.

Viral vectors, of which adeno-associated virus (AAV) and lentivirus are the ones used most often, contain a number of other materials when they are being made, such as empty capsids and virus aggregates, host cell proteins, nucleic acids, and buffers, toxicity agents, cryoprotectors, and surfactants. These likely are removed in the process, but there may be residual materials that Dr. Wilson said he believes can be inflammatory.

Most articles on gene therapy do not publish images of patients in whom a complication has developed. He described an image an eye of a nonhuman primate in a preclinical study of an AAV vector. The eye had pronounced inflammation at six weeks.

“This is a reaction that is expected and is not necessarily unanticipated, because a virus was injected that likely induced an immune response,” Dr. Wilson said.

He then showed data regarding adverse reactions recorded in the voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) trial. The agent was approved to treat inherited retinal diseases in patients with mutations in the RPE65 gene. In the trial that included 41 patients, the adverse reactions included subretinal deposits in 7%, eye inflammation in 5%, focal thinning in 2%, and foveal dehiscence in 2%.

In a small trial such as this, there is a 33% chance of not detecting a complication with a 1 in 100 frequency, Dr. Wilson explained.

“As doctors administering these treatments, we must be aware of adverse events that appear after the drug has been approved,” he advised.

Regarding cell-based therapies, Dr. Wilson showed an eye of a primate treated with autologous cells that were fluorescent; over time, the cells disappeared. “Even though these were autologous cells, there was an immune reaction, due to activation of the microglial cells in the eye of the animal,” he said.

**Cost of Therapies**

Inherited eye diseases are not rare. Dr. Wilson and colleagues conducted a recent study that found that 14% to 21% of new-onset legal blindness in Oregon results from an inherited eye disease (Plus One 2019; https://doi.org/10.1371/journal.pone.0220983).

“RPE65 is a very rare disease occurring in 1 in 100,000 individuals, but when the various inherited diseases are added up, the population becomes substantial,” he said.

For example, choroideremia occurs in 1 in 50,000, X-linked retinitis pigmentosa 1 in 25,000, and Stargardt’s disease 1 in 8,000 to 10,000.


Treatment of both eyes costs $850,000. A wide range in the quality-adjusted life years was seen between the two studies, that is, $80,000 to $640,000, because of different assumptions about the longevity of the effect of the drug.

Dr. Wilson went on to explain that if those amounts are applied to more common diseases such as Stargardt’s disease and spinal muscular atrophy, the respective costs are $30 billion and $100 billion, which rivals the Medicare budget (parts, A, B, and D) for 2018 of $731 billion.

“Cost will definitely be an issue as these very important agents are developed,” he said.

**Conclusion**

Dr. Wilson added that physicians and researchers must be aware of how their trials are conducted and that complications, such as surgical, immunologic, or wound healing, are reported so that ophthalmologists are aware that there is indeed potential for complications.

“Because of the high costs of development, alternative funding mechanisms will have to be found to bring these therapies to our patients,” he concluded.

**TAKE-HOME**

- The cost and complications of gene- and cell-based therapies need further study, giving researchers goals to shoot for.

**COST OF THERAPIES**

Inherited eye diseases are not rare. Dr. Wilson and colleagues conducted a recent study that found that 14% to 21% of new-onset legal blindness in Oregon results from an inherited eye disease (Plus One 2019; https://doi.org/10.1371/journal.pone.0220983).

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IN THE RACE AGAINST GLAUCOMA, DURABILITY WINS

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Delivering a new confidence.
Confocal microscopy: Seeing what does not meet the eye

Technology allows ophthalmologists to make rapid, accurate diagnosis

By Lynda Charters: Reviewed by Sophie X. Deng, MD, PhD

LIMBAL STEM CELL deficiency (LSCD) is an ocular surface disorder that results from decreases in the number and function of corneal epithelial stem and progenitor cells that results in the inability to maintain the normal homeostasis of the corneal epithelium.

LSCD signs include conjunctivalization and persistent epithelial defects with or without neovascularization, ocular surface inflammation, and scarring. The disease can be acquired non-immune-mediated, acquired primary immune-mediated, idiopathic, or inherited.

Diagnosis can be tricky because the disease presentation varies greatly with the degrees of severity of the stem cell deficiency, according to Sophie X. Deng, MD, PhD. This can range from stipping of the corneal epithelial layer to severe dry eye disease, to scattering in the early, intermediate, and late disease stages.

Along with the changes in density, the mean basal cell diameter increases in LSCD with increasing disease severity. Confocal microscopy can also measure the epithelial thickness. “The thicknesses of the corneal epithelium and the limbus decline gradually with the increasing severity of the stem cell deficiency,” Dr. Deng said.

A noteworthy point is that the subbasal nerve plexus disappears in LSCD of more advanced stages. She and her colleagues looked at 51 eyes of 37 patients with LSCD and found that there was almost a 47% decrease in the subbasal nerve plexus in the early stage of the disease, which continued to trend down in the intermediate and late stages. In addition to this finding, the tortuosity of the nerve increases with disease severity.

The imaging technology also can differentiate affected from unaffected corneal regions in the same eye.

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

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CASE REPORT: Dr. Deng recounted the case of a 61-year-old woman with bilateral LSCD that was diagnosed by a clinical examination. The patient was referred for limbal stem cell transplantation or a keratoprosthesis. Neovascularization was present in four quadrants and the corneas were opaque. Confocal microscopy showed that the corneal epithelium was normal and the limbal epithelium was present in three quadrants and not the nasal quadrant. The diagnosis was actually minimal LSCD and a living-related keratolimbal transplantation was planned.

SOPHIE X. DENG, MD, PHD:

†Data on file - includes trabeculectomy and tube shunt.

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Researchers taking aim at stem cell-based therapy for AMD

Treatment utilized to replace dying RPE with iPS-derived RPE

By Michelle Dalton

RESEARCHERS AT THE National Eye Institute (NEI) are launching a clinical trial to test the safety of a novel patient-specific stem cell-based therapy to treat geographic atrophy (GA), the advanced dry form of age-related macular degeneration (AMD), a leading cause of vision loss among people age 65 and older. The GA form of AMD currently has no treatment.

“The protocol, which prevented blindness in animal models, is the first clinical trial in the U.S. to use replacement tissues from patient-derived induced pluripotent stem cells (iPSC),” said Kapil Bharti, PhD, head of the NEI Ocular and Stem Cell Translational Research Section.

The therapy involves taking a patient’s blood cells and, in a lab, converting them into iPSCs, which have the potential to form almost any type of cell in the body. The iPSCs are programmed to become retinal pigment epithelial (RPE) cells, the type of cell that dies early in the GA stage of macular degeneration. RPE cells nurture photoreceptors, the light-sensing cells in the retina. In GA, once RPE cells die, photoreceptors eventually also die, resulting in blindness.

The therapy is an attempt to shore up the health of remaining photoreceptors by replacing dying RPE with iPS-derived RPE.

Before they are transplanted, the iPS-derived RPE are grown in sheets one cell thick, replicating their natural structure within the eye. This monolayer of iPS-derived RPE is grown on a biodegradable scaffold designed to promote the integration of the cells within the retina.

In 2014, NIH researchers developed a technique to speed up the production of stem-cell derived tissues. The method simultaneously measures the expression of multiple genes, allowing scientists to characterize cells according to their function and stage of development.

“Progress in stem cell-based therapies has been limited by our capacity to authenticate cells and tissues,” Dr. Bharti said.

The stem cells Dr. Bharti used to make RPE are iPS stem cells, which are produced by reverting mature cells to an immature state, akin to embryonic stem cells. iPSC cells can be derived from a patient’s skin or blood cells, coaxed into other cell types (such as neurons or muscle), and in theory, reimplanted without causing immune rejection.

To verify the identity of RPE made from iPSCs, scientists use microscopy to ensure the tissue looks like RPE and physiologically assays to ensure the tissue behaves like RPE. Quantitative measurement permits the simultaneous measurement of a few genes per sample, Dr. Bharti said. His group teamed up with Marc Ferrer, PhD, of NIH’s National Center for Advancing Translational Sciences to develop a multiplex assay—a method for simultaneously measuring multiple genes per RPE sample in a highly automated fashion.

The assay is based on a platform from the biotech company Affymetrix. In the assay, tiny snippets of DNA tethered to beads are used to capture RNA molecules—created when genes are expressed by cells in the RPE sample. Once captured, the RNA from distinct genes is labeled with a fluorescent tag.

In the animal study, Dr. Bharti describes tested the approach in rat and pig models. Ten weeks after the human iPSC-derived RPE patches were implanted in the animals’ retinas, imaging studies confirmed that the lab-made cells had integrated within the animal retina.

The transplanted cells functioned properly. Immunostaining confirmed that the iPS-derived RPE expressed the gene RPE65, suggesting the lab-made cells had reached a crucial stage of maturity necessary to maintain photoreceptor health. RPE65 is necessary for the regeneration of visual pigment within the photoreceptors and is an essential component for vision.

Tests showed that the transplanted RPE cells were pruning photoreceptors via phagocytosis, another RPE function that helps keep photoreceptors healthy. In addition, electrical responses recorded from photoreceptors rescued by RPE patches were normal. Photoreceptors treated with a control empty scaffold had died.

Under the phase I/IIa clinical trial protocol 12 patients with advanced-stage GA will receive the iPS-derived RPE implant in one of their eyes and be closely monitored for a period of at least one year to confirm safety.

A concern with any stem cell-based therapy is its oncogenic potential: the ability for cells to multiply uncontrollably and form tumors. In animal models, researchers genetically analyzed the iPS-derived RPE cells. They found no mutations linked to tumor growth.

The use of an individual’s autologous (own) blood cells is expected to minimize the risk of the body rejecting the implant. Should early safety be confirmed, later study phases will include more patients to assess the efficacy of the implant to prevent blindness and restore vision in patients with GA.

REFERENCE


KAPIL BHARTI, PhD
p: 858/263-1222
Dr. Bharti has no financial disclosures to report.

By Michelle Dalton

Researchers will take a patient’s own blood cells, and in a lab, convert them into iPS cells capable of becoming almost any type of cell in the body. In this case, the iPS cells are then programmed to become retinal pigment epithelial cells, the type of cell that dies early in the GA form of AMD. (Image credit: National Eye Institute)
AGE-RELATED MACULAR DEGENERATION (AMD) is the leading cause of blindness worldwide among the elderly, and its prevalence is expected to increase as the population ages. There are two forms of this sight-stealing disease: dry AMD and wet AMD.

Although wet AMD is chronic and incurable, the disease is manageable with anti-VEGF injections. Vision can be maintained, or even improve, with consistent, regular, anti-VEGF treatment. Both forms of AMD involve a complex interplay of pathogenic factors, including genetics and lifestyle risk factors such as smoking.

Research thus far has failed to decipher how these various factors interact in dry AMD and success in doing so would require a large-scale, collaborative and multidisciplinary approach.

To address this issue, a large-scale, collaborative, systems biology approach is needed to expedite the discovery of treatments for dry AMD—a leading cause of blindness among people 65 and older for which there is no treatment—according to a report by a working group of scientists appointed by the National Advisory Eye Council (NAEC).

The NAEC is a 12-member panel that guides the National Eye Institute (NEI), part of the National Institutes of Health.

The NAEC charged the working group to assess the state of research on dry AMD and to propose directions for future research.

“The working group thoroughly assessed what is known about dry AMD pathobiology, and the recommendations will be informative for considering future NEI research priorities to align with promising pathways for discovering therapeutic targets,” said NEI Director, Paul A. Sieving, M.D., Ph.D.

The NAEC acknowledged that drugs must first be developed for the dry AMD subtype that may impact disease progression and treatment efficacy by allowing physicians to see cellular and subcellular structures at different disease stages.

For example, “when used with a scanning laser ophthalmoscope and OCT, adaptive optics systems can visualize individual cones, changes in rods, RPE [subretinal pigmented epithelial], and SDD [subretinal drusenoid deposits] in dry AMD,” the researchers write.

Other novel imaging modalities suggested include polarization-sensitive OCT, fluorescence lifetime, and hyperspectral fluorescence.

They note, however, that more data and larger clinical trials are needed to confirm the utility of these new imaging technologies, as existing trials have been in small study populations with variable follow-up.

“To advance our understanding, we must identify imaging biomarkers of early changes that reflect AMD pathobiology, predict disease progression and/or treatment response, and correlate with molecular markers that are relevant in both animal models and humans,” they conclude.

What non-retina specialists need to know about dry AMD

Multiple genetic, environmental factors play in development of disease

By Michelle Dalton

### NEW IMAGING TECHNOLOGIES

Standard-of-care imaging for AMD diagnosis, classification of disease severity, and the evaluation of treatment efficacy currently include color fundus photographs, optical coherence tomography (OCT), and OCT-angiography. Handa et al. suggest that new imaging technologies could help identify preclinical risk factors or currently unknown AMD subtypes that may impact disease progression and treatment efficacy by allowing physicians to see cellular and subcellular structures at different disease stages.

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### PRECISION MEDICINE

Much like in patients with cancer, Handa et al. believe dry AMD can and should be treated through personalized, precision medicine. To do so, they advocate for individually tailoring computer models to assess a person’s potential risk for developing dry AMD, progression rate, and potential response to treatment.

For this to be effective, however, the group acknowledged that drugs must first be developed for the dry AMD population through robust clinical trials. They further recommend partnering with pharmaceutical companies to develop these trials, with patients followed closely long-term.

Finally, patients with dry AMD should be encouraged to donate their eyes to science after they die to further research efforts.

With these efforts and approaches, Handa et al. hope to expedite the research and development of dry AMD treatments.

### TAKE-HOME

- Although wet AMD is chronic and incurable, the disease is manageable with anti-VEGF injections. Vision can be maintained or even improve with regular treatment.

### REFERENCES


### UNDERSTANDING RISK FACTORS

There are multiple genetic and environmental factors at play in the development of AMD. More than 40 genetic variants have been associated with AMD, including APOE, CHF, and HTRA/ARMS2. The discovery of these gene variants have helped identify potential therapeutic targets, and gene therapy clinical trials are currently underway for the treatment of the wet subtype.

“We propose that researchers utilize a systems biology approach, integrating the big data available from clinical registries and various fields of biology known as ‘omics’ to develop better models and ultimately treatments for patients with this blinding disease,” said report co-author Joan W. Miller, MD., chair, Harvard Medical School Department of Ophthalmology, Boston.

“This approach would integrate basic, genomic, pre-clinical, medical, pharmacological, and clinical data into mathematical models of pathological processes at different stages of dry AMD in order to ask how relevant individual components act together within the living system,” Dr. Miller said.

JOAN W. MILLER, MD
P: 617/573-3925
Dr. Miller has no financial considerations to 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.

watch series at: ophthalmologytimes.com/insights/glaucoma-insights
A physician’s challenge: Getting paid in 2020 and beyond

Ophthalmologists finding that reimbursement is becoming increasingly difficult

By Todd Shryock

REIMBURSEMENT FOR INDEPENDENT physicians, including ophthalmologists, is getting more challenging each year. Between the ever-changing reporting requirements from CMS and contractual differences among commercial payers, just keeping up can be a full-time job.

Insurers are asking for more and more data to document patient outcomes and Medicare has its own reporting requirements through the Merit-based Incentive Payment System (MIPS). New payment models that emphasize primary care are in the works, so decisions physicians make today can affect their future income.

So what reimbursement trends should physicians expect in the near future?

CMS ADDS MORE EMPHASIS TO PRIMARY CARE

The biggest changes announced by CMS won’t take effect until 2021. The agency announced it has aligned its E/M coding requirements for office and outpatient E/M visits with those adopted by the American Medical Association CPT Editorial Panel. It is also retaining four levels of E/M codes for new patients and 5 levels for established patients. Earlier, CMS had proposed paying a single flat fee for E/M levels 2-4 and retaining a separate payment for level 5 visits.

There’s always been a notion that CMS would go back to fee-for-service, reset the payment model (away from MACRA), or allow them to coexist,” according to Ash Shehata, MHA, MBA, national sector leader for healthcare and life sciences for consulting firm KPMG. “2019 was the year of reality setting in.”

MIPS isn’t going away, but the number and types of APMs is not sufficient to move physicians out of it.

“The idea here is to move all physicians to more value-based payments. There are still large numbers of physician practices that are not becoming part of groups and remaining independent,” said Cheryl Damberg, PhD.

For 2020, the Medicare Physician Fee Schedule conversion factor includes a small increase from $36.04 to $36.09. The last of the increases for inflation that were part of MACRA occurred last year, and physicians are now facing a six-year period with no inflation update, meaning the conversion factor is not expected to grow in any meaningful way.

“The reason for this is CMS envisioned there would be more movement to more Alternative Payment Models (APMs) and value-based care arrangements, but we haven’t seen that transition to the degree Congress wanted when it passed MACRA,” according to Anders Gilberg, senior vice president, government affairs, for the Medical Group Management Association.

For those in MIPS, 2020 is an important year because of escalating penalties, says Gilberg.

“The potential bonus has yet to be determined (it was 1.65 percent last year) because it’s budget neutral, but it’s really important to focus on quality reporting in 2020 to avoid the negative payment adjustment in 2022.”

CMS always intended MIPS to be a feeder system into APMs that would have less reporting burdens and better-aligned financial incentives for each specialty, noted Gilberg, but the number of APMs is limited.

“The idea here is to move all physicians to more value-based payments,” explained Cheryl Damberg, PhD, distinguished chair of healthcare payment policy at The Rand Corp. “There are still large numbers of physician practices that are not becoming part of groups and remaining independent. CMS is trying to experiment and figure out how to get them into the game.”

Primary Care Plus establishes patient-centered medical home-like payments and cost efficiency measures, while Primary Care First, which launches in 2021, builds on that idea and adds monthly capped payments for patients.

While these new models may seem enticing, a practice needs to carefully consider why it would change its practice model. “For practices that are efficient and running a clean operation, they can make additional money,” said David Zetter, CHBC, founder and lead consultant at Zetter Healthcare Management Consultants. “They require proactive care management and the coordination of care—things most primary care practices do not do. You have to have a staff to handle this, and it is going to cost money. Do not go in blindly and think you are going to get extra money just by changing your model.”

He advises thinking about what effect changing to a new model would have on both patients and the practice, and what the impacts on cost and quality would be.

“Know your break-even point and if you will get a return on investment,” Zetter adds.

PRIVATE Payers CONTINUE TO PUSH FOR VALUE

Private payers have been increasingly paying for outcomes, and experts say this will not change in 2020 or beyond.

“Value-based care is where the excitement is,” said Shehata, who adds that private payers have been watching CMS experiment with more risk sharing and what results it has achieved. “If anything, what the CMS payment models have done is driven the industry to step up its capability to accelerate risk-sharing.”

In addition, provider networks are widening.

“It is no longer just the inpatient, outpatient, and outpatient E/M levels 2-4 and retaining a separate payment for level 5 visits.
and primary care providers," he added. "Now, they are bringing in pharmacy, home care, and the entire continuity of care."

Zetter explained that physicians need to pay attention to payment trends among private payers to make sure they are maximizing their reimbursement potential.

"Private payers are looking for the same things as Medicare: patient access, engagement, low costs, and quality outcomes," Zetter said. "They are looking for providers who participate in programs that meet all of those requirements."

If doctors aren’t paying attention to costs—by, say, sending patients to a nearby imaging center instead of one that’s farther away but in the patient’s plan—the plan’s administrators will take a dim view of the physician and possibly terminate the contract.

"Several years ago, United Health dumped thousands of providers with no notice," said Zetter. "They are allowed to do that if they do not think you are participating and meeting the plan requirements the right way."

Conversely, doctors who do exceptionally well with cost containment and patient satisfaction scores can be invited to join an exclusive provider organization and possibly earn bonuses.

"These are invite-only networks," Zetter said. Invites are high-quality, low-cost providers with good patient access, perhaps with evening or early morning hours. "Even in today’s age with retail clinics in competition, there are still primary care physicians that have banker’s hours and they wonder why they are not successful," he says. "You have to look at what is happening around you."

He said that to maximize reimbursement, doctors have to pay attention to data in their EHRs and what is happening around you. "Even in today’s age with retail clinics in competition, there are still primary care physicians that have banker’s hours and they wonder why they are not successful," he says. "You have to look at what is happening around you."

"A smaller practice, if they have a dedicated set of providers who are interested in providing value-based care, can be more nimble and do things more quickly if given the tools and resources to be more effective," Gilberg said. "We see success on both sides, but a small practice is still typically disadvantaged."

One way to minimize that disadvantage is to focus on either fee-for-service or value-based care, but not both, Gilberg added.

"If you are doing a little of both, the incentives do not align with one another," he said.

Another threat to small practice reimbursement is the rise of retail clinics.

"The expectation is that these will be more efficient," Shehata explained. "Before we see any effect on pricing, we will probably see a more meaningful effect on the customer experience. The expectation is that patients will be able to shop across the market, and I think that will drive pricing and create transparency."

Dr. Damberg said it is probably too early to know how retail clinics will affect reimbursement rates, but it’s something the industry is closely watching.

"Will they find less expensive ways to offer comparable services and maybe more conveniently?" Dr. Damberg said. "They may be in line with what the next generation’s tastes are and how they consume products versus the traditional old-school model for practices. If they can walk into a doctor’s office in a mall and immediately get primary care services, that’s a potential game changer."

One factor working in favor of physicians is their scarcity.

"People underestimate the limited supply of physicians, and health systems have to compete pretty aggressively to keep these people," Dr. Damberg added. "They have to stay competitive in how they negotiate with them, because they cannot afford to lose them."

The number of smaller practices is also proving to be a reimbursement challenge for a market that wants to push more risk to physicians as part of their contracts.

"There is still a lot of care provided by independent and small practices," Dr. Damberg concluded. "That is a big question mark for CMS and the commercial market in how to bring them along and control spending while still providing quality care."

EDITOR’S NOTE: This article originally appeared in Medical Economics, a sister publication of Ophthalmology Times.
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“Something is wrong with my husband’s vision – he keeps telling me my new hairdo is beautiful.”

Artwork by Jon Carter

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