Sustained-release implant offers long-term IOP control, preserved visual function

Bimatoprost SR represents a paradigm shift in glaucoma treatment

Leading up to this approval, the bimatoprost SR implant met the primary endpoint of the ARTEMIS phase III study. It lowered IOP by about 30% and was found to be noninferior to timolol for reducing IOP through 12 weeks. In extended follow-up, more than three-quarters of eyes did not require additional treatment for one year following three administrations of the drug.

In the ARTEMIS phase III trials, patients were randomly assigned to treatment with bimatoprost SR versus timolol. Two concentrations of bimatoprost were evaluated, 10 and 15 mcg. The focus of the results reporting was on the lower dose, which will be the one that will be commercially available. Eyes randomly assigned to bimatoprost SR received implants every four months, for a total of three implants of the drug over the course of one year.

“Eighty percent of the eyes that received the three implants of bimatoprost SR had sustained IOP control for one year, without the need for additional treatment,” said

Issue
Highlights

SURGERY
Novel tools for pediatric surgeons helping to optimize surgeries

IMAGING
Diagnosing LSCD noninvasively: SD-OCT preferred

CLINICAL DIAGNOSIS
Confocal microscopy key to diagnosing infectious keratitis

THERAPEUTICS
Laboratory tear tests: How to use them, determine reimbursement

DEVICE TECHNOLOGY
Presbyopia-correcting IOLs enhance customization, provide more options
Our greatest achievement yet, Contoura™ Vision outperformed even glasses and contacts.*\(^1\)

With the exceptional results for improvement in UCVA, BSCVA and visual disturbances, Contoura™ Vision Topography-Guided LASIK has taken refractive outcomes even higher.\(^1\) By enhancing the symmetry of the corneal surface, Contoura™ Vision stands alone in refractive precision — and it’s only from WaveLight®.

For additional information or to schedule a demonstration, contact your Alcon sales representative. For important safety information about this product, please refer to the adjacent page.

*Post hoc analysis of postoperative UCVA compared to preoperative BSCVA of 230 eyes contained in the FDA T-CAT pivotal trial at 12 months. The primary end point evaluated changes in BSCVA.
\(^1\) Results from FDA T-CAT-001 clinical study for Topography-Guided vision correction (with the 400 Hz ALLEGRETTO WAVE® Eye-Q Excimer Laser).
15 Confocal microscopy key to diagnosing infectious keratitis Rapid differentiation and management of infectious keratitis using in vivo microscopy can result in improved vision for patients.

16 AMD awareness: Close focus on preserving vision Early diagnosis is mandatory in order to begin preventative treatment.

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Bringing stability during trying times

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

MARCH IS THE MONTH of expectation as we prepare for spring. What typically would be ordinary is anything but ordinary in these times.

At MJH Life Sciences, we are working to ensure the safety of our staff, while continuing to provide information that is important to your practice. The Ophthalmology Times team continues to be the voice of reliable coverage of the coronavirus, detailing the facts without any hype. We continue to provide the latest ophthalmology-related information on social media. You also can find coverage online at Ophthalmology-Times.com/Coronavirus.

In this issue of Ophthalmology Times we have talked to several ophthalmologists to find out how COVID-19 is impacting their daily work. You will want to see how it is affecting your colleagues, and learn some tips that could help you in your work.

In this issue, we feature a special section titled “New Initiatives in Refractive Surgery,” which kicks off on the cover with an article with Roberto Pinelli, MD, from the Switzerland Eye Research Institute. He details new procedures to Richard L. Abbott, MD, who takes a look at reported outcomes with three different combinations of presbyopia-correcting IOLs. We also talk to David Teenan, FRCOphth, FRCSEd, tackles device technology, presenting an overview of a retrospective analysis of clinical and patient-reported outcomes with three different combinations of presbyopia-correcting IOLs. We also talk to Dr. Richard L. Abbott, MD, who takes a look at the incorporation of new technologies into clinical practices.

The therapeutics segment in this issue features the second article in a two-part series that discusses how to demystify tear osmolarity research and that offer a path forward through research.

What’s Trending

See what the ophthalmic community is reading on OphthalmologyTimes.com

1 Researchers reaching for the stars to cure presbyopia
OphthalmologyTimes.com/ReachingToCurePresbyopia

2 Li Wenliang: Ophthalmologist hero
OphthalmologyTimes.com/Coronavirus/LiWenliang

3 Effect of vaping on the eyes
OphthalmologyTimes.com/LetsChat/VapingEffect

eNewsletter


Video

Glauconix Biosciences’ Kimberly Southern (CEO) and Karen Torrejon, PhD (CSO) discuss using innovative platform technology to reduce the cost of ophthalmic drug development as well as the 2020 pipeline in the glaucoma and other eye-related diseases space, during the Glaucoma 360 meeting. Go to OphthalmologyTimes.com/Glaucoma360/Glauconix

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Ophthalmology Times is a physician-driven media brand that presents cutting-edge advancements and analysis from around the world in surgery, clinical diagnosis, therapeutics, device technology, imaging, and gene therapy to elevate the delivery of progressive eye health from patient to physician. Ophthalmology Times’ vision is to be the leading content resource for ophthalmologists.

Through its multifaceted content channels, Ophthalmology Times will assist physicians with the tools and knowledge necessary to provide advanced quality patient care in the global world of medicine.
Tell-tale conjunctival hemorrhages
How the eye may offer clues for forensic medicine

By Peter J. McDonnell, MD

IN A STORY that is a tragedy in so many ways, Jeffrey Epstein was accused of being a serial pedophile, allegedly luring underage females into situations in which they engaged in sex with Epstein and his famous friends.

Placed in a high-security federal detention center after his arrest and while under “suicide watch,” a series of incredible events ensued, according to news reports. He allegedly was not watched.

Against policy, he was left alone in his cell, and some of the video cameras that should have monitored him were inoperative and the videotapes from other cameras were lost. He was eventually found dead. The errors and/or negligence surrounding this death of one of the highest-profile prisoners in this country quickly led to conjecture as to foul play.

Family members, questioning the government’s conclusion that the death was the result of suicide, retained the services of a forensic pathologist. Michael Baden, MD, has challenged the official verdict of suicide, and interestingly (to me as an ophthalmologist) his reason for doing so has to do with the postmortem examination of Epstein’s eyes.

According to Dr. Baden, subconjunctival hemorrhages in the body make it more likely that the prisoner was a victim of strangulation and less likely that he hung himself in his cell.

I had never been aware that such hemorrhages could be helpful in determining cause of death. This really is a thing. The forensic literature points to conjunctival and facial petechial hemorrhages as hallmarks of asphyxial deaths:

“Consensus in the literature suggests that their pathogenesis is related to the combined effects of increased cephalic venous pressure and hypoxia damage to endothelial cells. Despite the common knowledge that they are neither predictable findings in all asphyxial deaths nor rare in natural, non asphyxial deaths, the belief persists that petechiae are corroborative evidence of asphyxia.”

Among 5,000 consecutive autopsies by the medical examiner in Dade County, Florida, conjunctival petechiae were noted in 227 (4.5%). These small hemorrhages were most frequently observed in those who died of natural deaths, followed by those who died from asphyxia, head injury, and central nervous system disorders. The incidence of conjunctival petechiae in victims of “homicidal asphyxiation” was 78%.

Cardiopulmonary resuscitation has also been suggested as a possible cause of these hemorrhages.

T W I S T S  A N D  T U R N S

My perspective—as someone who is not a forensic pathologist but has read some of the literature—is that the presence or absence of these conjunctival hemorrhages is not sufficient to determine cause of death or clearly distinguish suicide from homicide. It also makes more sense to me that these hemorrhages are more likely to be the result of mechanical vascular phenomena rather than due to some sort of “hypoxia damage” to endothelial cells in the last few moments of life.

All the data do certainly point to the knowledge that can often be gleaned by a careful examination of the ocular (conjunctival and retinal) microvasculature.

Given the twists and turns in this sad saga and the high profile of many of those implicated as having been involved in sordid activities, it is unfortunate that conclusive answers may not be forthcoming.

REFERENCES

COVID-19 sowing uncertainty as ophthalmologists adapt to challenge

Several physicians detail how coronavirus is impacting their daily work, travel plans

By David Hutton

AS COVID-19 CONTINUES to spread in the United States and internationally, the disease increasingly is becoming a cause for concern throughout the healthcare field, including the ophthalmology community.

As this issue goes to press, the World Health Organization (WHO) officially declared COVID-19 a pandemic, meaning it has spread to more than 100 countries.

COVID-19, which first sickened people in China in December, is thought to have passed from animals to humans, like many similar pathogens. The symptoms of the disease include cough, fever and shortness of breath. However, little is known about its origins, and there has been no confirmation of its origin by any peer-reviewed scientific research, academic expert or public health organization.

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases. Similar viruses cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), according to the WHO. The primary defense to keep the coronavirus from spreading includes basic steps such as washing hands with soap and water and avoiding close contact with anyone who is sick.

In the office, the virus can be spread by respiratory droplets. As a result, it is imperative for ophthalmologists to wear eye and nose protection. This can include goggles or an N-95 mask.

Peter J. McDonnell, MD, chief medical editor of Ophthalmology Times®, and director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, said it absolutely is a concern for ophthalmologists, optometrists, technicians, and everyone involved in the office visit.

“It will be important for all of us to screen patients at the time the appointment is made and or when they arrive (do they have any signs or symptoms consistent with flu, colds, etc.), have they traveled to affected areas, etc.,” he said. “Patients with risk factors present should be triaged appropriately.”

COVID-19 may cause other ocular signs and symptoms, including photophobia, irritation, conjunctival injection, and a watery discharge. These signs are predominantly self-limiting but may require supportive care. Ocular tears and discharge are a potential contamination source. The eye is also a route of exposure.

Should a patient present for conjunctivitis and also exhibit fever and respiratory symptoms including cough and shortness of breath, and who have recently traveled internationally, particularly to areas with known outbreaks, or with family members recently back from one of these countries, could represent cases of COVID-19.

Dr. McDonnell said he believes what will happen going forward depends very much on the scenario that unfolds in the United States.

“Things like elective cataract surgery will drop for a while, while patients with more urgent problems will present in our offices, hospitals and surgery centers and we will care for them while segregating them as much as possible from individuals with or suspecting to have the coronavirus,” he said.

William W. Culbertson, MD, professor of ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, said his office is trying to screen patients by phone contact, at the check-in desk, and when the technician sees them.

“If they have flu-like symptoms they are given a mask, and the doctor and other staff wear masks,” he said. “Sanitizer is used on the exam rooms furniture after seeing each patient.”

Dr. Culbertson added that there are more no-shows for both clinic exams and surgery. As for concern, he said he has a high level of concern for the virus becoming a prolonged, endemic threat for doctors and staff.

“As COVID-19 continues to spread throughout the United States and internationally, the disease increasingly is becoming a cause for concern throughout the healthcare field, including the ophthalmology community. As this issue goes to press, the World Health Organization (WHO) officially declared COVID-19 a pandemic, meaning it has spread to more than 100 countries. COVID-19, which first sickened people in China in December, is thought to have passed from animals to humans, like many similar pathogens. The symptoms of the disease include cough, fever and shortness of breath. However, little is known about its origins, and there has been no confirmation of its origin by any peer-reviewed scientific research, academic expert or public health organization. Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases. Similar viruses cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), according to the WHO. The primary defense to keep the coronavirus from spreading includes basic steps such as washing hands with soap and water and avoiding close contact with anyone who is sick. In the office, the virus can be spread by respiratory droplets. As a result, it is imperative for ophthalmologists to wear eye and nose protection. This can include goggles or an N-95 mask. Peter J. McDonnell, MD, chief medical editor of Ophthalmology Times®, and director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, said it absolutely is a concern for ophthalmologists, optometrists, technicians, and everyone involved in the office visit. “It will be important for all of us to screen patients at the time the appointment is made and or when they arrive (do they have any signs or symptoms consistent with flu, colds, etc.), have they traveled to affected areas, etc.,” he said. “Patients with risk factors present should be triaged appropriately.” COVID-19 may cause other ocular signs and symptoms, including photophobia, irritation, conjunctival injection, and a watery discharge. These signs are predominantly self-limiting but may require supportive care. Ocular tears and discharge are a potential contamination source. The eye is also a route of exposure. Should a patient present for conjunctivitis and also exhibit fever and respiratory symptoms including cough and shortness of breath, and who have recently traveled internationally, particularly to areas with known outbreaks, or with family members recently back from one of these countries, could represent cases of COVID-19. Dr. McDonnell said he believes what will happen going forward depends very much on the scenario that unfolds in the United States. “Things like elective cataract surgery will drop for a while, while patients with more urgent problems will present in our offices, hospitals and surgery centers and we will care for them while segregating them as much as possible from individuals with or suspecting to have the coronavirus,” he said. William W. Culbertson, MD, professor of ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, said his office is trying to screen patients by phone contact, at the check-in desk, and when the technician sees them. “If they have flu-like symptoms they are given a mask, and the doctor and other staff wear masks,” he said. “Sanitizer is used on the exam rooms furniture after seeing each patient.” Dr. Culbertson added that there are more no-shows for both clinic exams and surgery. As for concern, he said he has a high level of concern for the virus becoming a prolonged, endemic threat for doctors and staff. “It appears to be extremely contagious and potentially lethal to older people with existing pulmonary problems,” he said. “There is no natural barrier or end in sight. Not since World War II has there been such a potential for disruption of everyday existence.” He said. William W. Culbertson, MD

‘There is no natural barrier end in sight. Not since World War II has there been such a potential for disruption to everyday existence.’

—William W. Culbertson, MD

“Medical centers are prohibiting any air travel for doctors, including domestic flights.” According to Laura M. Periman, MD, an ocular surface disease expert and director of Dry Eye Services and Clinical Research in Seattle, the situation continues to change rapidly, and on a recent day, her office did several things differently.

“I have postponed all IPL and Dry Eye Clinic visits in this high prevalence area,” she said.

Dr. Periman noted that every physician and technician has a full hand-washing session before and after each patient encounter as well as frequent Purell touch ups in the lane when touching equipment.

“We use a no-touch technique for instilling drops and examining the eye,” she said. This can include the use of a cotton swab to check the lids, meibomian gland dysfunction, etc.

New patients are greeted warmly but handshakes are skipped. Dr. Periman noted that COVID-19 is now endemic in Washington.

“I have several friends from medical school on the front lines and the contagiousness and seriousness of infection and severity of illness is very concerning,” she said. “Several physicians are out on quarantine.”

According to Michael Raizman, MD, Massachusetts Eye and Ear, Harvard University, Boston, a lot has changed in recent weeks and continues to change daily. “Because Boston has an increasing number of COVID-19 cases there, restrictions are multiplying rapidly,” he said. “We are in the process of installing plastic barriers on our slit lamps that will provide some increased protection from droplet spread.”

Dr. Raizman also is screening patients by phone for symptoms of upper respiratory infections. He has seen a decline in patient traffic. During a recent day, he had about 15% of patients cancel appointments for exams.

Moreover, as physicians, Dr. Raizman noted that the profession interfaces with educational and government institutions and the restrictions imposed on them by those groups are increasingly stringent.

“Hospitals are restricting elective surgery,” he said. “Meetings of groups are restricted. A week ago it was no more than 200 people. Now, in some cases, it is no more than 10 people.”

Dr. Raizman added that some medical centers are canceling patient office visits entirely, unless the visits are urgent and cannot be rescheduled at a later date.

“Grand rounds and other educational activities are canceled or converted to video-conferences,” he said.

“Medical centers are prohibiting any air travel for doctors, including domestic flights.”

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Continues on page 8 :: COVID-19
COVID-19

(Continued from page 7)

She has seen an increase in travel-related issues. “Our high-attendance annual Washington Academy of Eye Physicians and Surgeons (WAEPS), scheduled for the end of March, has also been postponed,” she said. “I am limiting travel. I practice excellent hand-washing hygiene, avoid touching my face and eyes, and carry disinfecting wipes with me.”

Daniel Terveen, MD, an ophthalmologist with Vance Thompson Vision, which has six locations across the upper Midwest, said the offices have taken “significant measures” to reduce the risk of transmission. The locations have one team member at each door checking temperatures and asking travel or sick contact questions. If anyone has an elevated temperature, they are urged to contact their primary care provider.

Dr. Terveen said the office called every patient on its clinic schedule over the next months and instructed them to let them know if they have traveled through an airport in the last 14 days, and is offering to reschedule appointments that aren’t urgent.

The locations have one team member at each door checking temperatures and asking travel or sick contact questions. If anyone has an elevated temperature, they are urged to contact their primary care provider.

The offices also have increased cleaning procedures for common areas and are disinfecting the atrium and door handles frequently throughout the day. For ophthalmologists in the practice, travel plans also have been adjusted.

“All of the doctors have changed both international and national travel plans due to the virus,” Dr. Terveen said. “We have also instituted a travel policy for all employees.”

Uday Devgan, MD, FACS, is in private practice at Devgan Eye Surgery in Los Angeles and Beverly Hills. He also is clinical professor of ophthalmology at the Jules Stein Eye Institute at the UCLA School of Medicine and Chief of Ophthalmology at Olive View-UCLA Medical Center.

He noted that most of what his office does in ophthalmology is elective, particularly in his cataract and refractive surgery practice.

“Our surgery center is now closed for two weeks,” he said. “I have also closed my private practice clinic for two weeks. Again, we are taking it day by day, and heeding the advice of our leaders and trusted colleagues.”

Prior to deciding to close, Dr. Devgan said his practice has seen about 15% of its scheduled cataract and refractive surgery patients elect to reschedule their procedures.

“Keys are hand-washing, disinfecting the equipment thoroughly for each patient, and using gloves when touching near mucous membranes such as the ocular surface,” he said.

Dr. Devgan also is keeping a watchful eye on current restrictions as he looks toward future travel plans.

CONCLUSION

During this time of limited but rapidly expanding information, eyecare providers need to stay highly vigilant to recognize early manifestation of COVID-19, including the consideration of viral conjunctivitis as a possible early presentation of the disease.

Watching 24-hour news coverage of the situation can cause a twinge of fear. Yet society is not on the brink of doom. Taking modest and sensible precautions should keep most people safe. Still, all healthcare personnel, including ophthalmologists, should be aware of the disease and on the lookout.

Travel update: ARVO, ASCRS cancel 2020 meetings

With a number of annual meetings that often attract a global audience, organizations are taking a cautious approach with the cloud of COVID-19 looming, and several conferences have cancelled their planned events for 2020.

The Association for Research in Vision and Ophthalmology (ARVO) has cancelled its annual meeting, to have taken place May 1-7 in Baltimore. In a statement posted to the ARVO 2020 website, the organization said “the health, safety and well-being of the ARVO global community is our highest priority.”

“Reports from the Centers for Disease Control and Prevention (CDC), yesterday’s announcement by the World Health Organization (WHO) declaring a pandemic, numerous university and institutional travel restrictions and ever-increasing numbers of confirmed cases all provide a clear need to take this action,” said ARVO leaders in the statement.

Leadership also noted the lost opportunity to present the latest research, and announced it would offer additional communication in the coming weeks that will provide alternative presentation options as we continue to work through these details.

In cancelling the event now, ARVO said it wanted to provide all attendees with time to manage air travel and hotel reservations.

“We urge those who were planning to attend the annual meeting to expedite flight cancellations,” the statement said.

“Attendees who booked through ARVO housing do not need to do anything; reservations will be cancelled automatically. Individuals who booked reservations on their own should cancel them immediately.”

ARVO also will fully refund annual meeting registration fees for individuals that do not select an alternative presentation option when that information is released in the next two weeks.

The American Society of Cataract and Refractive Surgery (ASCRS) has cancelled its annual meeting, scheduled for May 15-19 in Boston. ASCRS announced the decision on its website.

The organization announced it decided to cancel the meeting “in the interest of public safety, after monitoring daily recommendations from the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), the Massachusetts Department of Public Health (DPH), and the City of Boston.”

In its statement, ASCRS said it would explore the possibility of rescheduling the meeting and will continue to offer online resources to support ophthalmologists’ ongoing clinical and networking needs. According to ASCRS, it has worked closely with the Boston Convention Exposition Center to navigate this very challenging and dynamic situation.

“During this entire process there has never been an option that was an ideal solution, but we ultimately feel this is the correct decision and in the best interest of our members,” the statement continued.

Other cancellations, updates

Vision Expo East, scheduled to be held March 26-29, will be consolidated with Vision Expo West in Las Vegas, Sept. 23-26. Ashley Mills, CEO of The Vision Council, organizers of the event, said it was a difficult decision for the organization.

“Ultimately The Vision Council’s Board of Directors believes the safety and well-being of our members, exhibitors, attendees and staff must come first,” she said. “Furthermore, we want to be respectful to the exhibitors and attendees who would not be able to attend Vision Expo East due to travel restrictions.”

Yancy Weinrich, COO of Reed Exhibitions, added that “Vision Expo East is a pivotal event that brings together a diverse industry to celebrate advances in eyewear, eyecare, technology and fashion. “Over the past year, our Vision Expo staff and the entire show community worked tirelessly to plan a completely reimagined show that we were looking forward to unveiling in March. This will now take place September 23-26 in Las Vegas and we’re excited for the show at that date.”

There are several high-profile shows this year, including the American Society of Retina Specialists annual meeting, July 24-28 in Seattle; and the American Academy of Ophthalmology (AAO) annual meeting, Nov. 14-17 in Las Vegas.

Regarding its annual meeting in Seattle, in a statement, ASRS officials said “leadership is actively monitoring developments concerning COVID-19 and staying abreast of updates from health organizations responsible for tracking and responding to the virus, including the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), Washington State Department of Health, and King County Public Health.

“In addition, we are closely monitoring all travel alerts issued by the U.S. Department of Homeland Security. As our meeting approaches, we will rely on these authorities to provide us guidance and take appropriate steps, if necessary, to ensure the safety of our participants.”

In the meantime, as this issue goes to press, ASRS officials are encouraging members to monitor the CDC website for additional information and recommendations for protecting themselves from an infection.

In a statement, AAO said, “It is monitoring the situation and advice from health authorities, and keeping our members and employees informed. The Academy meeting (AAO) is still [several] months away and it is too soon to know what impact it will have on attendance.”
REFRACTIVE SURGERY

ADVANCES CONTINUE TO PROGRESS FOR PHYSICIANS PERFORMING REFRACTIVE PROCEDURES

NEW INITIATIVES IN

This one-piece, hydrophobic, acrylic, ocular implant comprises an embedded opaque annular mask with a central aperture. Aligned light rays converge through the 1.36 mm central aperture while peripheral defocused and often aberrated rays are blocked from disrupting the image. As a result, patients experience a continuous range of vision from near to far, including the increasingly important intermediate range.

At 1.5 feet to 7 feet away, the intermediate range represents a critical zone of activity for most people. It is where we eat most of our meals, do most of our desk work and watch most of our large-screen media. It is where many people earn their livings, including refractive surgeons. Originally intended to be paired with a monofocal IOL, it has been found that when paired with a multifocal IOL, the IC-8 is better than previous alternatives at enhancing visual acuity at intermediate distances, and so has the potential to benefit this underserved cohort.

Likewise, patients who have had previous refractive procedures are becoming more common. As they proliferate, so does the necessity for techniques and technologies tailored to support their special needs. The IC-8 has shown good outcomes in these “veteran” surgical patients.

Surgeons are just now beginning to appreciate the additional benefits made possible by combining the small-aperture IC-8 lens with IOLs that function on completely different optical principles. Experimentation is ongoing, and this novel strategy may ultimately lead us to maximize the full potential of the IOL, providing patients with truly satisfying customized outcomes.

LOW-ADD MIOLS

Low-add multifocal lenses (MIOLs) have been shown to improve intermediate visual acuity and offer surgeons the ability to further individualize patients’ visual outcomes, particularly when mixed with other refractive technology.

Combining a multifocal lens with a different type of lens also can act to minimize glare and halo, an intrinsic characteristic of MIOL optics. It is well known that most types of presbyopia-correcting IOLs—including multifocal refractive and diffractive, and even the newest trifocal technology—sacrifice distance vision to some extent in order to correct near vision and induce a variable amount of dysphotopsias.

One study of the AcrySof ReSTOR +2.50 D IOL (Alcon) found it provided good intermediate and functional reading acuity at 38.9 cm. Eyes with the +3.00 D IOL had better intermediate vision than the +3.00 D IOL, providing patients with truly satisfying customized outcomes.

SMALL-APERTURE IOL

MAXIMIZING VISUAL ACUITY FOR PATIENTS

Ophthalmologists can customize visual outcomes

By Prof. Gerd U. Auffarth, MD, PhD, FEBO; Special to Ophthalmology Times

A n IOL (IC-8 IOL, AcuFocus) currently under FDA investigation, is a new small-aperture ocular implant that employs the pinhole camera effect to correct presbyopia.

By flattening the defocus curve on both the myopic and hyperopic sides, the device essentially creates a small amount of myopia, thereby extending the patient’s depth of focus and eliminating visual effects from corneal astigmatism or other irregularities.
those with the +4.00 D model without compromising distance and near visual acuity.

**MF EXTENDED DEPTH OF FOCUS**
The Lentis Mplus LS-313 MF20 (not available in the United States) is a foldable, one-piece, aspherical multifocal posterior chamber IOL that extends a patient’s depth of focus. Its refractive rotationally asymmetric design helps minimize the loss of light to below approximately 7%, thereby improving contrast and retinal image quality. An evaluation of the implant, with +2.00 D of near add compared with +3.00 D, found superior visual outcomes from far distance to a near of about 25 cm with the latter lend. The +2.00 D demonstrated excellent visual results from far distance to an intermediate distance of about 50 cm.

**ANCHOR WITH SMALL APERTURE APPROACH**
Unlike the multifocal implants described above, the IC-8 IOL from AcuFocus functions due to the pinhole effect: By reducing scattered light and permitting only parallel rays to reach the macula, depth of focus is extended and visual disturbances such as glare and halo are reduced. Small aperture technology can even overcome problems of corneal asphericity and irregularities. Astigmatism up to 1.50 D can be corrected with the lens alone.

Typically, the IC-8 IOL is implanted in the nondominant eye, with a multifocal lens in the contralateral eye. To enhance acuity, the small aperture IOL can be paired with other technology such as a multifocal, a low-add multifocal, or even a trifocal lens. There are many combinations to consider, with the basic idea being that using different types of implants can enhance the sharpness of vision at near, intermediate and distance and minimize the side effects of the competing technologies.

**SMALL APERTURE PLUS EDOF TECHNOLOGY**
The ongoing prospective multicenter Mosiac study was undertaken to evaluate visual outcomes from the combination of the IC-8 small-aperture IOL and the Lentis MF-20.(6) Our group presented 5-month follow-up data on 13 patients with bilateral implantation of the IC-8 IOL with the Lentis LS-313 MF-20 with +2.00 D of near add. We looked at parameters including:

- uncorrected and corrected (binocular) far, intermediate, and near visual acuity
- defocus curves
- Salzburg Reading desk
- photic phenomena (halo and glare simulator)

Included were the 26 eyes of 13 patients with cataracts whose average age was 68.5 ± 10.8 years. The targeted refraction for the IC-8 IOL eyes was -0.43 ± 0.18 D with an achieved refraction of 0.42 ± 0.41 D. The achieved refraction was within ±0.50 D 62% of the time. The targeted refraction for the MF-20 eyes was -0.15 ± 0.16 D, and the achieved refraction was -0.33 ± 0.42 D. The achieved refraction was within ±0.50 D 85% of the time.

We found that patients have excellent binocular visual acuity at far and intermediate distances, as well as functional vision at near. They further had functional reading acuity at near and intermediate distances, and there was a comparatively low incidence of photic phenomena.

The combination of the IC-8 IOL small-aperture implantation of a +2.00 D multifocal IOL like the Lentis LS-313 MF-20 is a good treatment option for patients who are motivated to achieve spectacle independence.

**IMPLICATIONS**
Multifocal lens designs can exhibit pronounced peaks and troughs, but the IC-8 IOL provides uninterrupted functional vision over 3.00 D of defocus. The small-aperture principle has the ability to produce a high quality, full-range of vision without blurry zones, and it is more forgiving of refractive error misses or surprises. The IC-8 IOL has been shown to provide good visual outcomes in post-LASIK and post-RK eyes, making it an attractive option for patients who previously could not find an appropriate presbyopia-correcting IOL. Likewise, patients with corneal irregularities can benefit from the technology’s ability to reduce aberrations.

**CONCLUSION**
When paired with MF EDOF technology, the IC-8 delivers excellent extended depth of focus at near, far and intermediate ranges while reducing halo and glare. It can enhance physicians’ ability to customize successful visual outcomes for each patient, even for those who’ve undergone previous refractive surgeries. Based on the simple, proven and ancient understanding of the pinhole’s effect on light ray alignment, the IC-8 IOL is a versatile tool to help cataract patients achieve their paramount post-operative visual goals.

**REFERENCES**
REFRACTIVE SURGERY

(Continued from page 1)

Over the past six years, we have been approaching corneal surgery in Lugano using a novel procedure that unites Femtolasik and transepithelial crosslinking.

This combined technique is known as Femtolasik Lux, and aims to increase the stability of the visual outcome in patients, thereby maintaining a healthy and robust cornea.

Femtolasik Lux is a non-invasive, “no-touch” procedure, which—at no point touching the eye with any instrument—uses three different light sources to resolve any visual defect in a few minutes without pain.

Although the chances of ectasia occurring have become very much reduced over the past decade, it nonetheless remains a very remote possibility to be avoided.’

– Roberto Pinelli, MD

This procedure leads to a final sharp refractive result, provides a stronger corneal tissue that is less vulnerable to curvature change, and reduces refractive error regression and incidence of corneal ectasia.

Safety, effectiveness, and excellent long-term results have been demonstrably achieved.

There is a protocol for this technique called the Lugano Protocol. ParaCel eye drops are used to soak the corneal epithelium for a time that can range from 30 to 50 seconds after the repositioning of the flap.

Soaking is thus customized and a very minimal quantity of riboflavin is delivered to the cornea in a short time, which is possible due to its osmotic properties.⁴

Exposure to UV-A is performed with Avedro technology at 30 mW/cm². This quantity of ParaCel and timing of exposure are enough to permit ParaCel to penetrate the flap and spread into the stroma.

Unlike other data reported in the current literature, we osmotically soak the cornea over the flap leaving the interface free from any possible irregularity due to riboflavin on the cornea.

The purpose is to take advantage of CXL treatment, usually performed to strengthen corneal tissue, in order to stiffen a prospective weakened cornea and prevent corneal ectasia, which is every refractive surgeon’s nightmare.

Although the chances of ectasia occurring have become very much reduced over the past decade, it nonetheless remains a remote possibility to be avoided. I am pleased to report that after our six years with this procedure, we have not experienced one case of ectasia.

As far as side effects are concerned, I believe that there are no adverse events to report and no flap wrinkles. (Figure 1)

It seems that the riboflavin penetration did not induce any refractive change. On the contrary, a greater stability and a better and softer crosslinking of the cornea were observed, and less regression, particularly regarding myopic astigmatism.

With ParaCel being osmotic, its penetration through the cap to the corneal stroma probably restores biomechanical strength to the cornea.

This aspect enables the flap to become better re-integrated into the cornea, becoming one with the other corneal layers, and thereby more stable and less susceptible to dislodging, unlike the situation in the past. I believe that this is why we don’t see any ectasia.

In addition to the assessment of post-operative visual data, the self-perceived satisfaction with the procedure was evaluated by our Psychology of Vision Unit: objective/subjective outcomes were found to be equally positive.

Researchers said their experience with Femtolasik Lux with the Lugano Protocol has also been positive, and they fully intend to continue with this technique in order to restore vision and improve the overall quality of life in our patients.

Miorica Bertelli, OD, Caterina Berti, OD, and Elena Scaffidi, MS, contributed to this report.

REFERENCES


special report

NEW INITIATIVES IN REFRACTIVE SURGERY

‘Although the chances of ectasia occurring have become very much reduced over the past decade, it nonetheless remains a very remote possibility to be avoided.’

– Roberto Pinelli, MD
New tools for pediatric surgeons to optimize surgeries

A wide range of technologies can impact outcomes in young ophthalmic patients

By Lynda Charters; Reviewed by Ken K. Nischal, MD, MBBS, FRCOphth

New devices for use in pediatric surgeries are making challenging procedures less so. Ken K. Nischal, MD, MBBS, FRCOphth, described how he benefits from use of the bag-in-the-lens (BIL), precision pulse capsulotomy, and integrated intraoperative optical coherence tomography (OCT) in children, whose tissues react differently from those of adults.

According to Dr. Nischal, the new technologies can positively impact the surgical outcomes in these patients.

**BIL**

This innovation, developed by Mary Jose Tassignon, MD, and colleagues in 2005 (Verh K Acad Geneesk Belg 2005;67:277-88), involves creation of one opening of the same size in both the anterior and posterior capsules. A lens that is grooved fits by placement of two leaves into the groove.

“This results in sequestration of the lens epithelial cells and thus elimination of opacification in the visual axis,” according to Dr. Nischal, division chief and professor ophthalmology, University of Pittsburgh and Children’s Hospital of Pittsburgh of the University of Pennsylvania Medical Center, Pittsburgh.

Dr. Tassignon developed foldable rings to ensure creation of a precise capsulotomy. The rings are placed on the capsule and covered with a viscoelastic agent and serve as a template to create the opening.

“If surgeons are having difficulties doing pediatric cataract surgeries, the rings can be used to get the correct sizing of the opening,” Dr. Nischal said. “Even though a child’s capsule is elastic, this works.”

A posterior capsulorhexis is created using the anterior opening as the template. He explained that in a 4-year-old child. The lens appeared the same two years postoperatively as it did on the first day postoperatively, with a perfectly clear visual axis.

There is a learning curve attached to this procedure, in that it can be difficult to get the two capsules anchored into the groove, Dr. Nischal noted.

**OCT FOR PEDIATRIC CATARACT**

Dr. Nischal believes integrated intraoperative OCT is helpful for planning and teaching and is especially helpful in complex cases. A benefit is that while looking through the microscope, the surgeon can see the OCT image and the surgical image in one ocular. He explained how he uses this technology in a number of different clinical scenarios.

While performing all of his pediatric cases, Dr. Nischal first removes the peripheral soft lens material, which differs to the approach in adult surgeries, and removes the nuclear material last.

“At this stage, if vitreous emerges, it can be tamponaded; remember congenital defects in the posterior capsule are much more common in children with cataracts,” he advised and pointed out that the OCT visualizes vitreous in real time, and because of this the need for air or triamcinolone staining is eliminated.

In the demonstration of a case, he tamponaded the vitreous with a viscoelastic agent and then converted the opening into a posterior rhexis and performed an anterior vitrectomy.

In cases of traumatic cataracts, using OCT, the surgeon can easily differentiate lens material from vitreous. “This integrated OCT is a very useful technology for that,” he stated.

Cases of intumescent cataracts are always problematic because of the presence of fissures filled with fluid that are under pressure. Upon entering the eye, the fluid is released rapidly, which results in a tear to the equatorial region. To counter this, Dr. Nischal simultaneously uses an irrigating cannula and an MVR blade or needle.

“When I enter the eye, I aspirate at 100%, which results in a controlled tear,” he said. This procedures eliminates the lakes of fluid, which helps control the surgery.

A pearl for performing pediatric surgery is recognizing that removal of the lens matter results in forward bowing of the posterior capsule due to positive vitreous pressure.

“In this scenario, the posterior capsule is being pushed into the anterior chamber,” Dr. Nischal said. “For novice surgeons learning pediatric cataract surgery, this is not readily apparent. I have seen many fellows enter the eye with an instrument and inadvertently hit the posterior capsule.”

**TAKE-HOME**

▶ New technologies provide better outcomes for pediatric patients.

‘This technology may become useful if it can be made to a small size to use with children.’

— Ken K. Nischal, MD, MBBS, FRCOphth

Using integrated OCT provides surgeons with a much better understanding of what is happening in the eye.

Another pearl involves creating a posterior capsulorhexis in children, which differs from adult cataract surgery where the posterior capsule is invariably left intact.

In children, an intact posterior capsule will opacify. Once a posterior capsulorhexis is done...
CXL imperative in treatment of pediatric keratoconus

Strategies lead to positive outcomes in tough cases

By Cheryl Guttmann Krader, BS, Pharm; Reviewed by Ken K. Nischal, MD

FINDINGS FROM STUDIES investigating the efficacy and safety of corneal collagen crosslinking (CXL) for keratoconus in pediatric-age patients and developmentally delayed adults and the consequences of leaving their ocular disease untreated provide a solid base of evidence for offering CXL to these populations, according to Ken K. Nischal, MD.

“In the United States, CXL is only approved for the treatment of progressive keratoconus in patients from 14 to 65 years of age, and so it may not be offered to younger children even if indicated,” said Dr. Nischal, professor of ophthalmology and chief, Division of Pediatric Ophthalmology and Strabismus, University of Pittsburgh Medical Center, Pittsburgh, PA.

Keratoconus is not uncommon, with incidence rates reported up to 265 per 100,000 patients. Unfortunately, disease onset tends to be in early adolescence, and these younger patients are at risk for rapid progression and a lifelong visual disability.

Dr. Nischal said his take on the issue is that technology should be for those who cannot advocate for themselves or who are the most vulnerable.

“Those individuals are the children and developmentally delayed adults,” he said. “In fact, there is mounting evidence that CXL should be offered to children at presentation rather than waiting for progression.”

After a review of several papers, Dr. Nischal cited a study by Chatzis and Hafezi that reported a progression rate of 88% after one year of follow-up in a series of 59 eyes of 42 children awaiting CXL for keratoconus.

A G R E S S I V E N A T U R A L H I S T O R Y

Several published studies demonstrate that keratoconus progresses at a rate that is much faster in children than in adults and that CXL arrests disease progression in pediatric patients, said Dr. Nischal.

Discussing some of these papers, he cited a study by Chatzis and Hafezi that reported a progression rate of 88% after one year of follow-up in a series of 59 eyes of 42 children awaiting CXL for keratoconus.

S U R G E R I E S

(Continued from page 12)

and the lens placed in the capsular bag, the viscoelastic is removed.

At this time, Dr. Nischal explained that the infusion bottle is lowered so that the pressure of the infusion does not push the IOL through the posterior capsular opening into the vitreous.

C O M P L E X C A S E

Finally, he described a highly complex case of a 4-year-old boy who ran into the end of a kitchen knife, which resulted in a traumatic cataract and scarring and the need for a corneal transplant and cataract removal.

Dr. Nischal planned a dual surgery, which would not have been possible before OCT was integrated into the process, which visualized the stalk between the damaged lens and the scarred cornea.

This allowed the severing of the stalk and inflation of the anterior chamber with viscoelastic.

Dr. Nischal said the cataract was removed, an IOL placed in the bag and the corneal graft completed.

“The availability of this technology changed the outcome for this child,” he concluded.

KEN K. NISCHAL, MD, MBBS, FRCOPHTH

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Dr. Nischal reported receiving honoraria from Carl Zeiss Meditec Inc.
Another study by Leon-Mesplie et al. showed that children who did not have CXL for keratoconus had a sevenfold increased risk of requiring a keratoplasty compared to adults.2

“If you do not want to do CXL in a child, you certainly do not want to have to perform penetrating keratoplasty considering the extra problems that it brings in terms of operative and postoperative issues,” Dr. Nischal said.

Other papers in the peer-reviewed literature show the safety and benefit of CXL for keratoconus in pediatric patients. In what is the largest published study to date, Padmanabhan et al. analyzed data from 194 eyes of 153 children ages 8 to 18 years old that underwent CXL for documented progressive keratoconus.3

Of the 194 eyes, 142 had CXL using the standard Dresden protocol and 52 were treated using hypoosmolar riboflavin.

The CXL was associated with keratometric thinning and stabilization of pachymetry during follow-up extending to 6.7 years. Of the total cohort, 59 eyes were followed for longer than 4 years, and reversal of keratometric flattening occurred in 14 (24%) of those eyes.

“Interestingly, however, the flattening did not correlate with significant changes in vision or corneal pachymetry,” Dr. Nischal said.

‘Not performing CXL and therefore leaving them to possibly develop hydrops from progressive corneal thinning and lose vision makes their lives and and the lives of their families much worse.’

— Ken K. Nischal, MD, MBBS, FRCOphth

Findings from a study by Mazzotta et al. suggest that regression after CXL may be more likely in patients with severe allergy who are eye rubbers.4 These investigators reported outcomes for 62 eyes of 47 patients ages 8 to 18 years who underwent CXL and represents the report with the longest post-CXL follow-up for a pediatric population.

The outcomes were stable at 10 years in 80% of eyes. A 2 D increase in mean keratometry occurred in four eyes of two patients who had severe ocular allergy and were eye rubbers, but stability was achieved after repeat CXL. No other patients in the series needed a repeat treatment because of CXL failure.

Two papers have reported on performing CXL for keratoconus in developmentally delayed patients.5,6 Dr. Nischal noted that the patients, who often have Down syndrome, already have challenges

“Not performing CXL and therefore leaving them to possibly develop hydrops from progressive corneal thinning and lose vision makes their lives and the lives of their families much worse,” he said.

BARRIERS AND SOLUTIONS

Reluctance to perform CXL in children and developmentally delayed adults may be partly due to concern that they will not remain still during a procedure performed using local anesthesia. In addition, children and developmentally delayed adults may not comply with instructions to avoid eye rubbing that not only increases the risk of regression over time but also the chance for infection following the procedure.

To overcome these problems, Dr. Nischal said that he performs CXL in most pediatric patients and developmentally delayed adults under general anesthesia with a regimen that will result in complete paralysis.

“If there is not complete paralysis, the eye may roll up during the UV light application, leaving me grabbing for forceps to try to hold the eye in place,” he said.

Dr. Nischal said he uses integrated intraoperative OCT (Carl Zeiss Meditec) to assess adequacy of the riboflavin soak.

AN OCT scan prior to the soak allows for baseline evaluation and after the soak there is a visible change in reflectivity on the OCT. The OCT is also used after UV exposure.

“If I see a clear interface after the UV light application, I know I am going to get a good result, but I do not yet have enough follow-up to know what the outcome is in cases where I cannot see the interface,” he said.

To protect the eye in the early post-treatment period while the epithelial defect is healing, he usually places a temporary central tarsorrhaphy for two days and prescribes topical moxifloxacin six times daily to be applied at the medial canthus.

“So far, we have not had any cases of infection, and the children seem comfortable with the tarsorrhaphy in place,” Dr. Nischal said.

Patients who had CXL elsewhere with placement of a bandage contact lens reported much less pain and discomfort with their second eye procedure using tarsorrhaphy.

One case involved a developmentally delayed patient whose parents were very frightened about the child tolerating the second eye procedure.

“The parents reported that with the lids stuffed shut, the child did not touch the eye and was very relaxed,” Dr. Nischal said.

Dr. Nischal is aggressive with treatment for allergic conjunctivitis-related inflammation both pre- and post-CXL as a strategy to mitigate eye rubbing. Patients are also referred for behavioral therapy to reduce eye rubbing.

REFERENCES


Confocal microscopy key to diagnosing infectious keratitis

Rapid diagnosis, treatment can result in improved vision

By Lynda Charters; Reviewed by Pedram Hamrah, MD, FACS

In vivo confocal microscopy has become valuable in diagnosing and following infectious keratitis. For ophthalmologists, an important advantage is that the technology facilitates more rapid diagnosis compared with other diagnostic modalities. This can be instrumental in saving vision.

The technology is also well suited to following patients over time to monitor treatment progress, according to Pedram Hamrah, MD, FACS.

Dr. Hamrah is director, Center for Translational Ocular Immunology, New England Eye Center, Tufts Medical Center, and professor of ophthalmology, Tufts University School of Medicine, Boston.

Two in vivo confocal microscopy machines are in use although not commercially available. A slit-scanning confocal microscope (ConfoScan 4, Nidek Technologies) uses a white light to visualize corneal structures and has decreased scanning time. The other machine, a laser scanning confocal microscope (Heidelberg Retina Tomography, Heidelberg Engineering), uses a 600-nanometer laser. The machines are capable of imaging structures layer by layer from the epithelium to the endothelial cells.

These diseases can be diagnosed a few ways. The gold standard is by culture, which provides a definitive diagnosis, although a specimen can be difficult to obtain from deep tissue and may provide a low yield, and days to weeks are needed to reach a definitive diagnosis. Corneal biopsy also provides a definitive diagnosis if the result is positive. The downsides are that there is potential for a sampling error and the procedure is invasive. Polymerase chain reaction (PCR) requires corneal scraping and may have a low yield, and days to weeks are needed to reach a definitive diagnosis. Corneal biopsy also provides a definitive diagnosis, although a specimen can be difficult to obtain from deep tissue and may provide a low yield, and days to weeks are needed to reach a definitive diagnosis. Corneal biopsy also provides a definitive diagnosis if the result is positive.

After treatment, in vivo confocal microscopy can be used to monitor patients’ progress. “Using confocal microscopy, the cyst density decreases after treatment. In our experience, the rate of surgical interventions has decreased by following these patients,” Dr. Hamrah reported.

**Fungal Keratitis**

These pathogens are differentiated based on the appearances of the various species involved. *Fusarium solani* is characterized by filamentous structures, *Ruecklingia bilacatus* by curved structures, *Aspergillus* structures are 5 to 10 μm in diameter with septate hyphae with dichotomous branches and 200 to 400 μm long, and *Candida parapsilosis* has sausage-like structures 10 to 40 μm long and 5 to 10 μm wide.

In addition to the shapes, the angles of the structures differ among the various pathogens, with *Aspergillus* and *Fusarium* structures at 45- and 90-degree angles, respectively.

The fungal structures can be difficult to differentiate from stromal nerves, which have a more regular branching pattern and are larger at 25 to 50 μm.

The sensitivities (>89%) and specificities (78% to 100%) for diagnosing fungal keratitis are better than those for acanthamoeba.

**Other Forms of Keratitis**

*Nocardia* keratitis is a filamentous bacterium characterized by multiple short, beaded structures with right-angled branching and is 10 to 30 μm in diameter. Filamentous structures generally clump together and are visible in the epithelium and stroma. *Microsporidia* keratitis appears as clusters of epithelial cells with bright borders in a rosette pattern. This bacterium is hyperreflective with pinpoint ovoid intracellular bodies and dot-like structures in surrounding epithelial areas. *Pythium insidiosum* keratitis has hyperreflective double-walled filaments of various sizes. Two shapes have been documented: some hyperreflective lines are beaded and string-like, 3.5 to 7.5 μm in diameter, and can be as long as 400 μm long with mean branching angles of 78.6 degrees; other hyperreflective lines can be thin ranging from 1.5 to 2.8 μm in diameter and 150 to 370 μm long. This pathogen does not respond to anti-fungal therapy and surgery is usually needed, Dr. Hamrah pointed out.

Bacterial keratitis has a nonspecific appearance.

Dr. Hamrah concluded that acanthamoeba and fungal keratitis can be diagnosed rapidly and safely by in vivo confocal microscopy, which shortens the time from presentation to onset of treatment, and decreases in the number of cysts or fungal elements are observed with treatment. Cysts appearing as chains or clusters indicate proliferative disease. Use of confocal microscopy for rapid diagnosis or monitoring of the treatment response may have the potential to improve the visual outcomes, and the technology also may help diagnose *Nocardia*, *microsporidia*, and *Pythium keratitis*.

The situations in which confocal microscopy is helpful include unresponsive and atypical keratitis, culture- and PCR-negative keratitis, graft rejection versus recurrent infection in grafts, neurotrophic keratopathy, crystalline keratopathy, and guidance for medical and surgical management.

**TAKE-HOME**

- In vivo confocal microscopy seems to be clinically useful for differentiating and managing infectious keratitis.

**Acanthamoeba cysts appear in confocal microscopy images as spherical, round, ovoid, or pear- or egg-shaped hyperreflective structures.**

- The cysts have a double-walled or star-shaped appearance and are 10 to 30 μm in diameter. Trophozoites are generally 25 to 40 μm and hard to see using the Confoscan but visible using laser confocal microscopy in untreated patients. Laser confocal microscopy also is sufficiently powerful to differentiate among cysts, leukocytes, and lymphocytes, but differentiating epithelial cells can be problematic.

- “When comparing cysts and trophozoites, cysts can be seen best in clusters or chains,” Dr. Hamrah said. “However, once viewed, the clusters or chains are generally poor prognostic factors. They are signs of proliferation or represent a lack of response to therapy. In that case, surgery or a change of therapy may be indicated.”

- The specificity and sensitivity of in vivo confocal microscopy are generally good, with specificities exceeding 76%, while the sensitivity can be lower. Studies from Moorfields Eye Hospital, London, and Massachusetts Eye and Ear, Boston, have reported lower sensitivities with less experienced operators.

- After treatment, in vivo confocal microscopy can be used to monitor patients’ progress. “Using confocal microscopy, the cyst density decreases after treatment. In our experience, the rate of surgical interventions has decreased by following these patients,” Dr. Hamrah reported.

**Diagnosis and Management**

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**Clinical Diagnosis**

By Lynda Charters; Reviewed by Pedram Hamrah, MD, FACS

Pedram Hamrah, MD, FACS

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

Dr. Hamrah has no financial interest in any aspect of this report.
AMD awareness: Close focus on preserving vision

Early diagnosis is mandatory to start preventive treatment

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

WITH AWARENESS OF the development of AMD increasing slowly amid an advancing age of the population, Prevent Blindness America is striving to educate the nation about the potential life-altering effects of the disease if left diagnosed and untreated.

According to Raul N. Khurana, MD, in line with an aging population, there has been an explosion of AMD. He is clinical associate professor in ophthalmology, University of California Medical Center, San Francisco and partner at Northern California Retina Vitreous Associates, Mountain View, CA.

“The estimated numbers of individuals with AMD will grow from the current 2 million patients affected to nearly 4.4 million by 2050, that is, over a doubling of the number of people with AMD,” he said.

In addition to that statistic, a Harris poll conducted by the American Academy of Ophthalmology (AAO) uncovered the jarring fact that individuals do not know that they can lose vision to an eye disease that initially has no symptoms.

The results of a retrospective cross-sectional survey published in BMJ Open Ophthalmology (Parfitt et al. 2019; http://dx.doi.org/10.1136/bmjophth-2019-000276) emphasized this. The study found that “only one third of respondents [members of the UK Macular Society] were able to self-detect symptoms. In line with national guidance, more than half (n = 131; 64%) of those self-detecting symptoms sought help promptly. For those whose initial diagnosis was delayed more than one week, 27% had potentially treatable wet AMD requiring urgent treatment to prevent vision loss. Reasons for delay reflected individual and service-related issues, including AMD not being detected in the initial consultation, and individuals not perceiving the urgency for symptom investigation.”

Dr. Khurana underscored two important points. First, that in the face of such a clinical scenario, early diagnosis is mandatory to start preventive treatment with high-dose antioxidant vitamins that may help prevent development of the vision-threatening complications of AMD.

“These vitamins decrease the chances of developing wet AMD,” he explained.

Second, if those complications do develop, the earlier a diagnosis is established, the better the treatment outcomes may be.

“This are the two reasons for raising awareness of AMD,” he said.

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IMPLANT

(Continued from page 1)

Felipe Medeiros, MD, PhD. distinguished professor of ophthalmology and the Joseph Wadsworth Endowed Chair, Duke University, Durham, NC. “We currently believe that the higher concentration of the drug achieved at the target tissues, such as the ciliary body, may lead to greater expression of matrix metalloproteinases and more extensive extracellular tissue remodeling, potentially explaining the long-term effects in reducing IOP.”

In addition, visual field data indicated that the eyes treated with the 10-µg dose of bimatoprost SR had less glaucomatous progression of the visual fields over time.

“We observed a significant difference at the one-year follow-up examination compared with timolol,” said Dr. Medeiros added. Specifically, at the one-year time point, the eyes treated with timolol had significantly faster progression in the visual fields with a change in the mean deviation of -0.80 decibel per year, he noted.

The implant was found to be safe. Most adverse effects were associated with the preparatory procedure for the administration of the implant. Some patients reported a burning sensation and redness that were mostly present within two days after administration, most likely due to the topical application of betadine. After two days, the most common side effect was conjunctival hyperemia.

A concern was the effect the implant on the anterior chamber may have on the corneal endothelial cells. “When bimatoprost SR was administered three times in four-month intervals, we observed that there was on average about a 5% to 6% loss of endothelial cells after 20 months of follow-up, but no measurable difference in the corneal thickness,” said Dr. Medeiros.

Dr. Medeiros added that there are multiple ongoing clinical trials to evaluate other dosing schemes.

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MISINFORMATION

Part of the misconception about AMD is that people have seen friends and family lose vision from the disease and the assumptions are that this is a result of the aging process as well as an absence of available treatments, which is no longer the case.

“These reasons could not be further from the truth. It is not normal to lose vision with aging in the absence of an associated condition, and many new treatments for AMD have become available in the past decade that allow patients to live productive lives after diagnosis because of the treatments,” Dr. Khurana said.

The AAO recommendation is that all people should have a dilated eye examination annually starting at age 40; individuals over age 65 with otherwise healthy eyes should have an examination from one to two years, or at intervals recommended by the individual’s ophthalmologist or optometrist.

Numerous organizations and industry are involved in educating the public about the dangers of AMD and their own methods of disseminating information via press releases, television advertisements and the like. In addition to Prevent Blindness, a volunteer organization dedicated to preserving vision, and the AAO, others include the National Eye Institute, Zeiss, Bausch + Lomb, and CooperVision, to name a few. A visit to their websites provide helpful information to patients about steps that can be taken to preserve vision.

“The more people who become aware of the inherent dangers of untreated AMD, the better the chances are of saving vision,” Dr. Khurana concluded. “This starts not only with physicians but also patients and the general public as well.”

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Dr. Khurana has no financial interests in any aspect of this report.

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Dr. Medeiros is a consultant to Allergan, Aerie, Aerie Pharmaceuticals, Bausch + Lomb, and CooperVision, to name a few industry companies.
INDICATIONS AND USAGE
DURYSTA™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION

Contraindications
DURYSTA™ is contraindicated in patients with: active or suspected ocular or periocular infections; corneal endothelial cell dystrophy (e.g., Fuchs’ Dystrophy); prior corneal transplantation or endothelial cell transplants (e.g., Descemet’s Stripping Automated Endothelial Keratoplasty [DSAEK]); absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; hypersensitivity to bimatoprost or to any other components of the product.

Warnings and Precautions
The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

Adverse Reactions
In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5%-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

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

References: 1. Allergan receives FDA approval for DURYSTA™ (bimatoprost implant) the first and only intracameral biodegradable sustained-release implant to lower intraocular pressure in open-angle glaucoma or ocular hypertension patients (press release). Dublin: PR Newswire; March 5, 2020.

IOP=intracocular pressure.
The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

Indocine Angulus: Following administration with DURYSTA™, the intracameral implant is intended to settle within the inferior angle. DURYSTA™ should be used with caution on patients with narrow indocine angles (Shaffer grade >3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with epothilonic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution on aphakic patients, in pseudophakic patients with a tom posterior lens capsule, or in patients with known risk factors for macular edema.

Intraocular Inflammation: Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Pigmentation: Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Endophthalmitis: Intracocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

Adverse Reactions

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

The most common ocular adverse reaction observed in two randomized, active-controlled clinical trials with DURYSTA™ in patients with OAG or DHT was conjunctival hyperemia, which was reported in 27% of patients. Other common ocular adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photosophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurry, and iritis. Ocular adverse reactions occurring in 1-5% of patients were anterior chamber cell lacrimation increased, corneal edema, aqueous humor leakage, iris adhesions, ocular discomfort, corneal touch, iris hypopigmentation, anterior chamber flare, anterior chamber inflammation, and macular edema. The following additional adverse drug reactions occurred in less than 1% of patients: conjunctival hyperemia, posterior capsule, pupil, vitreous, lens, lacrimation increased, corneal edema, aqueous humor increased, and iritis. Ocular adverse reactions occurring in 1-5% of patients were irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurry, and iritis. Ocular adverse reactions occurring in 1-5% of patients were irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurry, and iritis. Ocular adverse reactions occurring in 1-5% of patients were irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurry, and iritis.

The most common nonocular adverse reaction was headache, which was observed in 5% of patients.

Use in Specific Populations

Pediatric Use: There are no adequate and well-controlled studies of DURYSTA™ administration in pediatric patients due to the risk of implant migration into the posterior segment or hyperpigmentation to bimatoprost or any other components of the product.

Endophthalmitis: In the pre/postdevelopmental development study, oral administration of bimatoprost to pregnant rats from gestation day 7 to lactation day 7 resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from DURYSTA™; based on plasma Cmax). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA™; based on plasma Cmax). Lactation: There is no information regarding the presence of bimatoprost in human milk. No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA™; based on plasma Cmax).

DURYSTA™ is contraindicated in patients with active or suspected ocular or periocular infections; corneal endothelial cell dystrophy; prior corneal transplantation, or endothelial cell transplants; absent or ruptured posterior capsule; eye trauma or eyelid surgery within 1 month of implantation; and in patients with uncontrolled intraocular hypertension (OHT).

Pregnancy: There are no adequate and well-controlled studies of DURYSTA™ administration in pregnant women to inform a drug associated risk. Oral administration of bimatoprost to pregnant rats and mice throughout organogenesis did not produce adverse maternal or fetal effects at clinically relevant exposures. Oral administration of bimatoprost to rats from the start of organogenesis to the end of lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant exposures.

In embryofetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 1770 times the maximum human bimatoprost exposure following a single administration of DURYSTA™ (based on plasma Cmax; blood-to-plasma partition ratio of 0.858). In a pre/postdevelopmental development study, oral administration of bimatoprost to pregnant rats from gestation day 7 to lactation day 7 resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from DURYSTA™; based plasma Cmax and a blood-to-plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA™; based on plasma Cmax).

Lactation: There is no information regarding the presence of bimatoprost in human milk, the effects on the breastfeeding infant, or the effects on milk production. In animal studies, topical bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when DURYSTA™ is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for DURYSTA™ and any potential adverse effects on the breastfed child from DURYSTA™.

Pediatric Use: Safety and effectiveness of DURYSTA™ in pediatric patients have not been established.

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

Nonclincial Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human exposure [based on plasma Cmax; levels; blood-to-plasma partition ratio of 0.858]). Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the in vitro mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (1770-times the maximum human exposure, based on plasma Cmax; levels; blood-to-plasma partition ratio of 0.858).

Patient Counseling Information

Treatment-related Effects: Advise patients about the potential risk for complications including, but not limited to, the development of corneal adverse events, intraocular inflammation or endophthalmitis.

Potential for Pigmentation: Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent.

When to Seek Physician Advice: Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Rx only

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MARCH 15, 2020: Ophthalmology Times

TODAY, PHYSICIAN PRACTICES have significant familiarity with the principles of value-based care. However, other practice priorities often take precedence over evolving into value-based reimbursement relationships. But focusing on the principles of value-based care can benefit physician practices as they make informed diagnoses, as well as their patients and the health system.

Starting with four areas of focus informed by the EHR, practices can propel their organization toward real results in improving patient health while simultaneously reducing the risk of hospital admissions or re-admissions.

1. ANNUAL WELLNESS VISITS

Much of the success or failure of population health programs relies on proactive outreach. Such outreach can seem beyond the capabilities of some primary care practices. But as the patient’s most frequent point of contact with the healthcare system, the primary care practice plays a key role—one might say the key role—in the success or failure of a population health strategy.

2. CHRONIC DISEASE MANAGEMENT

While the wellness visit is a great opportunity to uncover emergent chronic conditions, the physician practice plays a central role in helping patients manage their conditions following diagnosis.

One way to help patients effectively manage chronic disease once it is diagnosed is by using the EHR’s disease registry capability to create and maintain lists of patients with chronic conditions, which can then be used to identify areas where gaps in care exist.

3. PREVENTIVE CARE

Even if patient is not diagnosed with a chronic condition, they could be identified as “at risk” through regular screening. Early identification will help the practice put measures in place to keep a closer eye on their well-being and health status.

As importantly, documentation of preventive care aids in ensuring quality metrics are captured in the EHR for public reporting under the CMS Quality Payment Program, which adjusts practice payment based on performance in areas of quality, cost, interoperability promotion and improvement activities.

4. MANAGING TRANSITIONS

Patient follow-through on the discharge plan of care and follow-up with the primary-care physician are critical to an optimal recovery following a hospitalization. A clear process for handing-off the discharged patient from the inpatient care team to the primary care physician facilitates the transition back to the community and provides early identification of complications or barriers to following a plan of care. The success of these handoffs helps avoid re-admissions or trips to the emergency room.

These strategies offer numerous benefits. Patients are better able to manage their health conditions and risks. Finally, demonstration of these competencies through quality and outcomes data positions the primary care practice as a good partner in managing patient health and risks to patients, payers, and purchasers alike.
Presbyopia-correcting IOLs enhance customization

Range of powers, optical designs creating plenty of options for patients

By David Teenan, FRCOphth, FRCSEd; Special to Ophthalmology Times

As the largest provider of premium IOLs in the United Kingdom, Optical Express has a long history of using advanced technology to help patients see and function well after surgery. With the proliferation of new presbyopia-correcting IOLs, we have offered patients a range of options over the years, from bilateral high, low or mid-add multifocal IOLs to extended depth of focus (EDOF) IOLs, and various combinations of these technologies.

Recently, we conducted a retrospective analysis of clinical and patient-reported outcomes with three different combinations of presbyopia-correcting IOLs. We looked at a large data set of patients who had undergone bilateral lens surgery at Optical Express over a four-year period between 2015 and 2018 and who had at least three-month follow-up. We compared three different lens combinations used during this time period: 3,362 patients with bilateral Tecnis Multifocal +2.75 (the lowest available add power for this lens); 1,250 patients with the Tecnis Symfony EDOF lens in one eye and the Tecnis Multifocal +2.75 in the other; and 665 patients with Symfony in one eye and the mid-add Tecnis Multifocal +3.25 in the other.

Demographic characteristics and preoperative refractions were similar among all three groups. The lens groups were not random, however. Lens selection was determined preoperatively, based on conversations with the patient about his or her visual requirements and goals, as well as anatomical or optical factors relevant to the decision. We conducted a four-year retrospective analysis of clinical and patient-reported outcomes with three different combinations of presbyopia-correcting IOLs.

CLINICAL RESULTS

Subjects did very well with all three lens combinations. At three months, 62.4% were seeing 6/5 (20/16) or better and 86.4% were seeing 6/6 (20/20) or better binocularly at distance without correction. There were no statistically significant differences in the rate of 20/20 uncorrected distance visual acuity (UDVA) among the groups. The Symfony/3.25 group was more likely to have 20/40 or better UDVA. At the three-month timepoint studied in this analysis, some patients may still have had residual refractive error. Secondary procedures to enhance the refractive effect, if necessary, had not yet been performed.

Uncorrected near visual acuity (UNVA) was N6 (J8) or better in 73.4% of all patients, regardless of the lens combination. The Symfony/3.25 and bilateral 2.75 groups were more likely than the Symfony/2.75 group to have UNVA of N6 (J8) or better.

The manifest refraction spherical equivalent (MRSE) was very good, with 76.6% of all patients being within 0.5 D of emmetropia. The bilateral 2.75 patients were statistically significantly more likely than either of the EDOF/multifocal combinations to be within 0.5 D. In terms of corrected distance visual acuity (CDVA), more than 90% of patients gained lines or maintained the same CDVA after surgery. Of all the patients, 16.9% lost one line of vision; 2.3% lost two lines; and 0.5% lost more than two lines. There was no statistically significant difference among the groups in the loss of > two lines. There was no difference in complication rates, so safety was excellent with all three IOL combinations.

PATIENT-REPORTED OUTCOMES

Overall, patients with all three IOL combinations were happy with their outcomes, with 90.9% being satisfied or very satisfied, and even higher percentages saying they would have the procedure again or recommend it to friends and family. There was no statistically significant difference between groups in the satisfaction rate.

Overall, more than half the patients reported experiencing no postop glare, halo, or starburst at all. At the other end of the spectrum, as we have come to expect with presbyopia-correcting IOLs, approximately 18%-20% of patients reported moderate to severe glare, halos, and starbursts after surgery. Although I expected to see a lower rate of photic phenomena in the EDOF/multifocal combination groups, this turned out not to be the case. Rates for moderate to severe symptoms were similar across all three groups. However, we would expect to see these decrease by six or 12 months postop, due to neuroadaptation and (where needed) enhancements.

Some patients experienced symptom resolution after surgery while others worsened, similar to what has been reported in other large studies of refractive procedures. About 15% of all patients reported a two-point increase in the symptoms compared to preoperatively, while 10-12% reported a decrease in symptoms from preop to postop. About 9% of patients reported moderate to severe difficulty with night driving after surgery; about 6% said night driving worsened postop compared to preop. Patients in the bilateral 2.75 group were least likely to report no glare, but otherwise, patient reports of visual disturbances and night driving experience were quite similar across the three groups.

TAKE-HOME

Retrospective data analysis reveals that several different combinations of certain IOLs provide excellent results.

TAKE-HOME

Retrospective data analysis reveals that several different combinations of certain IOLs provide excellent results.

IMPLICATIONS FOR PRACTICE

Although all three IOL combinations produced good results and would be good options for patients, the

(Chart courtesy of David Teenan, FRCOphth, FRCSEd)
Caution key when embracing new technologies in clinical practice

Patient safety, efficacy remain primary concerns for ophthalmologists

By Lynda Charters; Reviewed by Richard L. Abbott, MD

THE INCORPORATION OF a new technology into clinical practice runs the gamut of possibilities. Some embrace it, some shun it, others just don’t know what to do.

“How do surgeons decide when is the right time to proceed with learning a new surgical procedure or adopting a new technology?” asked Richard L. Abbott, MD. He is professor emeritus, Francis I. Proctor Foundation, University of California-San Francisco and secretary-general, Academia Ophthalmologica Internationalis. There is no correct answer to this question. The actual decision is based on the individual’s comfort level, risk tolerance, outcomes data on safety and effectiveness, and how he or she views new procedures or techniques, and the willingness to assume some risk, he commented.

KEY CONSIDERATIONS

Dr. Abbott presented a series of thought-provoking questions that can help clinicians take the plunge or step back momentarily from the water’s edge:

■ When deciding whether to adopt a specific technology, does it improve the quality of care? This question can be answered by determining if the technology improves the outcomes, if there are fewer associated complications, and if there is less risk to the patient.

■ Does the technology under scrutiny improve efficiency in delivering care? Specifically, does the technology save time, reduce the chances for a medical or surgical error, and have less staff requirements?

■ Does the technology make financial sense? The surgeon should understand the impact of the technology on the work and patient flow in offices and clinics as well as the spatial and environmental requirements.

NAVI GATING THE PATH

With those questions as a backdrop, the American Academy of Ophthalmology provided a view of Focal Point-Cataract Surgery that may clear the picture: “Innovations appear with such rapidity that sound statistical analysis of efficacy often lags well behind new product development. Frequently, new technologies and treatments are spearheaded by aggressive industry-sponsored marketing efforts rather than evidence-based research. A healthy skepticism is warranted in most instances for claims of superiority of new technology over older, well-established products and techniques that have proven safety and efficacy records.”

ETHICAL CONSIDERATIONS

The informed consent process involves accurate representation of the procedure and sufficient information for the patient to make an educated decision. This includes disclosure of the potential risk and complications of a procedure. The risk may be mitigated, however, by the presence of a mentor.

The surgical learning curve can be steep, with adequate experience gained with fewer cases. It also can be long, with adequate experience requiring more cases.

The system to learn new procedures is one of apprenticeship, with an organized curriculum and abundant resources that include courses, wet labs, and faculty supervision. With proper training, the complication rate associated with trainees, compared to experienced surgeons, is not necessarily higher (Ophthalmology. 1989;96:1225-7).

Following formal training, learning continues with self-study, enlist a mentor, careful patient selection, and providing a thorough informed consent. In addition, credentialing through a course, private practice, or a university, as well as learning complication management, all adds to the competence of the physician, Dr. Abbott explained.

Finally, when considering a new technology, conflicts of interest, both economic and non-economic, and their impact on decisions should be recognized. “Recognize and manage factors that potentially influence your recommendations; that is, enthusiasm for superiority of a new method, interest in expanding one’s surgical repertoire, reputational benefits, financial benefits, and possible academic benefits,” Dr. Abbott advised. All of this can help ensure physicians are prepared for virtually anything.

When incorporating new techniques into practice after residency, there are ethical responsibilities to patients, colleagues, and oneself,” Dr. Abbott concluded. “We take an incremental approach to adopting a new technology.”

CUSTOMIZATION

(Continued from page 19)

bilateral low-add multifocal group had the best near vision outcomes and seemed to be the more highly preferred option by both surgeons and patients.

We are fortunate to have presbyopia-correcting IOLs in a range of add powers and optical designs that provide the opportunity to customize the IOL choice to the patient needs. Based on the data in this analysis, I tend to rely most heavily on bilateral low-add multifocal IOLs for the majority of my patients. Implanting the same lens bilaterally helps to cut down on patients comparing the IOL performance between their two eyes. However, there are certainly still patients for whom it may make sense to personalize the refractive outcome by combining two different IOLs. In particular, this may be warranted when the results of the first eye are not as desired. I usually implant the nondominant eye first. If the patient is dissatisfied with the near vision or already symptomatic with glare and halo, for example, I might choose a different lens for the dominant second eye.

Given that the lens pairs in this study were selected by the surgeon as the best combination for each patient, it is also possible, of course, that patients in each group were relatively equally satisfied because the lens combination was appropriately tailored to each group’s varying needs and expectations. Ultimately, there is no substitute for talking to the patients about their visual demands and expectations, understanding the pros and cons of each presbyopia-correcting IOL available to us, and identifying the best match between the two.
Tear tests in eye care: Use, reimbursement outlined

Tear osmolarity reimbursement: Billing practices, how insurers decide what to pay

By Michael Berg

Editor’s Note: This is the second installment of a two-part series. Part 1 appeared in the Feb. 15 issue of Ophthalmology Times, page 16.

Eye-care specialists are quickly adopting in-office diagnostics including in vitro diagnostic, or laboratory, point-of-care tests to analyze tear fluid as front-line tools to triage refractive and refractive cataract patients. To help further clarify use and payment of these tests, the second part of this article discusses how the tests are implemented in practice and how reimbursement is determined.

OD ALERT: LAB TESTS ARE BILLED TO MEDICAL INSURANCE

Osmolarity and MMP-9 tests bill as a laboratory, pay under the laboratory fee schedule and always from the patient’s medical insurance. Although ocular surface disease (OSD) has an impact on both vision and medical care, in either case, laboratory testing will be billed under the medical plan—“a standard practice for most MDs.”

Optometrists, on the other hand, may be performing laboratory tests during a vision visit. Although the eye-care provider cannot conduct a medical and vision exam on the same day, he or she can perform and bill for a laboratory test during a vision visit. The vision visit is billed to the vision plan and the laboratory test to the patient’s medical plan.

During the vision exam, if the patient indicates symptoms on a dry eye questionnaire, the provider can perform and bill a lab tear test on the same day to confirm or rule out dry eye disease. If the patient has hyperosmolarity or abnormal MMP-9 and OSD is suspected, the patient can be rescheduled for a follow-up visit.

If a patient presents with dry eye symptoms during a vision exam, he or she should be informed that laboratory testing is recommended and discuss how OSD can have a negative impact on vision. Patients making a significant financial investment in cataract or refractive surgery, eyeglasses, or premium contact lenses should have the most accurate diagnostic data, refraction, and prescription possible to prevent refractive “surprise.” Staff should alert the patient that to ensure optimal outcome, a lab test will be performed and billed under their medical insurance, which may require an unanticipated out-of-pocket copayment.

Patients visiting an ophthalmologist’s office are usually older with the visit typically related to a medical problem—often under Medicare. If the patient is under Centers for Medicare and Medicaid Services (CMS) Medicare Part B, CMS will pay 100% of all lab tests to the provider with no patient copay or deductible, making it seamless with no financial impact to the patient. CMS currently pays $22.48 for each eye for the TearLab Osmolarity test (CPT 88361) in all 50 states.

CMS assesses appropriate payment for new laboratory CPT codes at an annual public meeting held every July. During this process, stakeholders, including manufacturers, physicians, or the pertinent clinical society, provide information regarding the type of technology, time, resources and cost involved to perform the test. The new test is compared to an existing, similar test on the Clinical Laboratory Fee Schedule.

Once an existing and comparable test is identified, the new test is given the same reimbursement as is being paid for the existing test. This crosswalk process is usually considered fair and equitable by both CMS and the stakeholders.

Commercial payers do not have such a process, however, and historically have adopted the CMS laboratory fee schedule’s rates. There is a caveat. The vast majority of laboratory tests are performed by a few large reference laboratories, such as Quest and LabCorp.

Because of this discount, insurance companies prefer and may require patients to only be tested at the reference laboratory. If a doctor’s office wishes to perform lab tests in the office, the insurance company will usually allow it, but only at the same discounted reimbursement they pay the contracted lab.

Tear fluid tests, however, such as osmolarity and MMP-9, can never be performed at an outside lab because the fluid sample is too small and fragile to transport. As pricing is dictated in the provider contract, each doctor would have to address a change in the contract on a case-by-case basis in order to “curve-out” special pricing for testing tear fluid samples.

TearLab’s Reimbursement Support team can help with reimbursement issues for osmolarity testing, as it regularly interfaces with insurance companies on behalf of customers. Though not easy, renegotiating can be discussed on a case-by-case basis.

CONCLUSION

Eye-care providers should first evaluate an in-office lab test or any other diagnostic procedure based on its clinical value and its impact on patient care in their practice. Once clinical value is established, economics can be assessed. Osmolarity and MMP-9 are now included in several professional groups’ clinical guidelines for the diagnosis and management of dry eye and OSD, providing justification for payers to reimburse these tests appropriately.

The Sjögren’s Syndrome Foundation recommends osmolarity testing as an advanced method to diagnosis and monitor a patient’s response to therapy, and the American Academy of Ophthalmology’s Preferred Practice Pattern indicates that osmolarity is an earlier indicator of clinical signs of dry eye, not inconsequential for a disease that may take three to six months of treatment to fully resolve.

Finally, as highlighted in part 1 of this article (OphthalmologyTimes.com/therapeutics/lab-tear-tests-aide-reimbursements-clinical-application-dry-eye), the American Society of Cataract and Refractive Surgery’s algorithm considers osmolarity and MMP-9 tests essential for pre-diagnostic assessments, ultimately stating that patients with visually significant disease should not proceed with cataract surgery.

TAKE-HOME

Eye care providers should evaluate an in-office lab test or any procedure to gauge its impact on patient care.

REFERENCES


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Michael Berg is vice president of regulatory and reimbursement, TearLab Corp.
Change the outlook for dry eye disease

Only CEQUA™ features NCELL™, an innovative technology that helps improve the ocular penetration of cyclosporine.

**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.

Visit GetCequa.com to learn more.

- NCELL helps improve the delivery of cyclosporine to where it is needed.
- Significant improvement in tear production at 3 months.
- Significant improvement in corneal staining as early as 1 month.
- In a comfort assessment at 3 minutes post instillation, 90% (Day 0) and 85% (Day 84) of patients had no or mild ocular discomfort.
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.

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.

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

**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.

**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.

**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.

**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 reinserted 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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PLR-00035 2016
Effects of atropine for controlling myopia progression in children

Range of unanswered questions may be addressed by ongoing research

By Cheryl Guttman Krader, BS, Pharm; Reviewed by Donald Tan, MD

AN ABUNDANCE OF evidence from randomized, controlled clinical trials supports the use of topical atropine to prevent myopia progression. Study results also show that using a low dose of atropine minimizes adverse effects and myopic rebound after treatment discontinuation. In addition, the findings indicate that the pharmaceutical formulation affects efficacy, said Donald Tan, MD.

Now, research in this area is continuing and is investigating not only the use of atropine for preventing myopia progression, but also whether it can prevent or delay the onset of myopia. Dr. Tan is adjunct professor in ophthalmology, Duke-National University of Singapore Medical School, and Visiting Senior Consultant, Singapore National Eye Centre, Singapore.

Over a period of two decades, the SERI completed five randomized controlled trials on myopia progression involving about 1,900 children, including two studies investigating atropine [ATOM1 (Atropine for the Treatment of Myopia) and ATOM2].

Now, SERI is conducting ATOM3 that is testing atropine as intervention to prevent or delay myopia onset in children.

Discussing atropine treatment as a pharmaceutical strategy for myopia control to address the global myopia burden, Dr. Tan said, “A Cochrane systematic review published in 2011 identified over 180 published interventional studies for approaches to reduce myopia progression.”

“These studies tested or are testing atropine in concentrations ranging from 1% to 0.005% in eyedrop, gel and ointment formulations and as standalone treatment or with adjunctive therapies that include orthokeratology, soft bifocal contact lenses, ketorolac, ace manisodiamine and acupuncture,” he said.

BRIEF HISTORY

Studies investigating topical atropine began in Asia in the 1970s. Despite the long-term history of use and evidence of its efficacy, the mechanism of action by which atropine may control myopia is unknown, Dr. Tan said.

“Initially it was thought that atropine might block accommodation, but that is now known not to be true,” he said.

The current concept is that it works either through a neurochemical cascade that begins with muscarinic receptors at the retina or via a non-muscarinic mechanism involving a direct effect on scleral fibroblasts mediated by inhibition of glycosaminoglycan synthesis. Dr. Tan is chair of the previous ATOM studies. ATOM1 was a two-year interventional trial launched in 1999 that compared atropine 1% with placebo in children ages 6 to 12 years old with –1 to –6 D myopia.

The results showed that atropine significantly reduced myopia progression and its effect on refraction strongly correlated with a reduction in increase of axial length.

However, the treatment was associated with significant side effects, and 1 year after it was stopped, significant rebound of both axial length and spherical equivalent were observed.

To try to minimize treatment-related side effects, ATOM2 tested lower doses of atropine: 0.5%, 0.1% and 0.01%. It enrolled children aged 6–12 years with –2–2 D of myopia.

The trial had a one-year washout period following two years of treatment, and atropine 0.01% was restarted for two years in any child whose myopia rebounded during the washout.

Results from ATOM2 demonstrated that both atropine-related ocular adverse events and myopic rebound decreased with decreasing dose.

The study also found that restarting atropine treatment the 0.01% formulation was able to reverse myopia progression that occurred during the washout year.

“At the end of five years, treatment with atropine 0.01% was associated with a 50% reduction in myopia progression,” Dr. Tan said.

Based on epidemiological evidence that a younger age of onset is associated with higher degrees of myopia measured both by higher SE and longer axial lengths, ATOM3 is designed to test whether intervention with atropine can prevent or delay the onset of myopia.

ATOM3 is enrolling children aged 5–9 years whose lowest distance corrected spherical equivalent was between +1 and –0.49 D and who have at least one parent with myopia. They are being randomized to receive 0.01% atropine or placebo. Treatment will be continued for 2.5 years and then children will be followed during a 1-year washout period.

A network meta-analysis of randomized controlled studies investigating interventions for myopia control in children published in 2016 by Huang et al. found that moderate and high dose atropine markedly slowed myopia progression.

In 2017, Gong et al. published a meta-analysis that included 19 studies of atropine involving more than 3100 children. The investigators concluded that the data showed the efficacy of atropine was dose-independent within the dose range studied, whereas the adverse effects were dose dependent, increasing with increasing dose.

In 2017, the American Academy of Ophthalmology Technology Assessment Committee issued a report on atropine for preventing myopia progression in children. The group reviewed 17 studies, of which eight were level I or II, and concluded that lower doses of atropine were slightly less effective than higher doses but were associated with less myopic rebound and fewer side effects. Among currently ongoing studies, three are being conducted in the United States.

THE FORMULATION EFFECT

The Low-concentration Atropine for Myopia Progression (LAMP) study compared atropine 0.01%, 0.025% and 0.05% versus placebo in children with myopia.

Results collected after two years indicated that the highest concentration studied was most effective. Dr. Tan observed that the efficacy of the 0.01% concentration in ATOM2 for reducing refractive change was more similar to that seen in the LAMP group treated with atropine 0.025% while the effect of the 0.01% concentration on axial length in ATOM2 almost equaled that achieved using the 0.05% concentration in LAMP. Pupil dilatation was also almost twofold greater in the ATOM2 atropine 0.01% group than in the atropine 0.01% group in LAMP.

“We do not know yet what the best formulation will be,” Dr. Tan concluded. “More studies are needed, and certainly there are a lot ongoing.”

DONALD TAN, MD
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This article was adapted from Dr. Tan’s presentation at the American Academy of Ophthalmology 2019 annual meeting. He is a consultant to pharmaceutical companies sponsoring studies of atropine treatment for myopia progression.
Ophthalmology Briefing: Expert Guidance on IOP Targets and Ocular Health in Glaucoma

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Characterize current intraocular agents used to treat glaucoma according to efficacy, safety, and preservative content
- Describe the common effects of long-term BAK on the conjunctiva, cornea, lens, and trabecular meshwork
- Evaluate the efficacy and safety of alternative preservatives and preservative-free formulations for the management of intraocular pressure

ACTIVITY

The aim of glaucoma treatment is to control intraocular pressure (IOP) to maintain patients’ visual function and quality of life. For primary open-angle glaucoma (POAG), the most common initial intervention is medical therapy. When treating POAG, clinicians establish a target pressure for each patient that is likely to meet these goals. The American Academy of Ophthalmology notes that sufficient data on risks and benefits of particular IOP targets are not currently available. Clinicians must estimate the target pressure—which is the upper limit of the desired protective range—based on each patient’s individual needs, considering factors such as:

- stage of glaucoma-related damage, such as structural optic nerve injury or functional visual field loss;
- the patient’s baseline IOP associated with damage;
- prior rate of progression;
- patient age;
- awareness that an overly aggressive target may expose the patient to costs and side effects of unnecessary medical or surgical therapy.3

DISCLOSURES (DR SMITH)


The staff of PER® have no relevant financial relationships with commercial interests to disclose.
Oluwatosin U. Smith, MD, of Glaucoma Associates of Texas, notes that the target pressure must also incorporate the side effect profile and convenience of use associated with resulting therapies, so patients will be more likely to adhere to their IOP-lowering regimen.

“Because IOP reduction currently is the only known way of treating glaucoma, (our goal) is to try and reduce IOP by 25% to 30% from baseline. But sometimes, 25% to 30% may not be adequate depending on what your starting point is,” she says.

“If a patient comes in with a pressure of 45 mm Hg, and I did a 30% reduction of IOP, I would still be at 30 mm Hg, which would be too much. In that case, leaning on either the Advanced Glaucoma Intervention Study or the Collaborative Initial Glaucoma Treatment Study, I usually tend to use (a target pressure) somewhere in the low to upper teens. I could start at the upper teens for somebody who started at such a high pressure,” she says. “But for somebody who comes in with milder disease based on optic nerve findings and visual field loss or structural loss, then I would be more accepting of a higher target IOP.”

A goal or target intraocular pressure is not a life-long number. It should be adjusted based on the patient’s initial evaluation, and then progressively or continuously throughout the patient’s disease as needed. —OLUWATOSIN U. SMITH, MD

The Advanced Glaucoma Intervention Study included adults aged 35 to 80 years with open-angle glaucoma that could not be adequately controlled on medications. The authors categorized 738 eyes into groups based on IOP averaged over 6-, 12-, and 18-month visits: < 14 mm Hg, 14 to 17.5 mm Hg, and > 17.5 mm Hg. Eyes in the highest-pressure group had an estimated worsening of 1 unit of visual field defect score greater during subsequent follow-up versus the lowest-pressure group.

The Collaborative Initial Glaucoma Treatment Study included 607 patients with newly diagnosed open-angle glaucoma. During 5 years of follow-up, those randomized to initial medical treatment had average IOP of 17 to 18 mm Hg, and those in the initial trabeculectomy group had average IOP of 14 to 15 mm Hg. At 4 years of follow-up, the groups had similar visual field loss, and at 4 years, the groups had similar visual acuity.

ISSUES AND DEVELOPMENTS IN MEDICAL THERAPY FOR POAG

Multiple classes of topical medications that lower IOP by 15% to 33% by increasing aqueous humor outflow or decreasing aqueous humor production are available for patients with primary open-angle glaucoma. However, topical therapies for glaucoma can be associated with ocular surface concerns. A literature review including 95 studies implicated prostaglandin analogs, β-adrenergic antagonists, alpha-adrenergic agonists, and topical carbonic anhydrase inhibitors—either due to the active ingredient or added preservatives—in new-onset or worsening ocular surface disease. The prevalence and severity of dry eye were associated with greater number of glaucoma medications used, and severity of ocular surface disease also appeared to be associated with longer duration of therapy. In addition, use of glaucoma medications for more than 3 years and use of 4 or more glaucoma medications have been identified as risk factors for failure of trabeculectomy surgery with mitomycin (respective HRs and 95% CI: 2.78, 1.8–9.6; 4.8, 1.2–28). For some patients, the presence of preservatives may be a consideration in choosing topical therapy. Benzalkonium chloride (BAK), a common component of eye drops, kills microorganisms via cell membrane lysis. It has been associated in laboratory research with proapoptotic effects in conjunctival epithelial and corneal cell lines, toxicity in trabecular meshwork cells, and inflammation in lens epithelial cells, and clinical evidence shows tear film changes. Switching patients from BAK-containing glaucoma therapies to BAK-free options—these include travoprost 0.004% and tafluprost 0.0015%—has been linked to a drop in dry eye lubricant use.

A number of recently approved and investigational pharmacotherapies with different modes of delivery to address IOP in glaucoma include:

Bimatoprost implant. The FDA approved this biodegradable implant in March 2020. In the two phase 3 ARTEMIS studies, patients with OAG or ocular hypertension (n = 1122) received the implants or twice-daily topical timolol 0.5% drops. During the 12-week primary efficacy period, the bimatoprost group had IOP reduction of approximately 30% from baseline, meeting the criteria for noninferiority. The most common ocular adverse reactions reported were conjunctival hyperemia (27% of patients); foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, increased IOP, corneal endothelial cell loss, blurred vision, and iritis were reported in 5% to 10% of patients.

Bimatoprost Ocular Ring. This drug-releasing ocular ring is designed for placement into the upper and lower fornices. Phase 2 data showed that in patients with open-angle glaucoma or ocular hypertension who were randomized to receive a bimatoprost ocular implant or twice-daily timolol 0.5% solution for 6 months, the bimatoprost treatment met criteria for noninferiority in diurnal IOP reduction at 2 of 9 time points. The bimatoprost group had a higher percentage of ocular and non-ocular treatment-emergent AEs; most ocular AEs were mild to moderate in severity.

Travoprost Intraocular Implant. In phase 2 testing, 74 patients in an interim cohort received either a faster or slower travoprost-eluting implant or topical timolol 0.5% solution. During 12 months, patients with implants had an approximately 30% reduction in mean IOP versus baseline. They also had a lower mean number of glaucoma medications (0.54 to 0.56 vs 0.72 in the timolol group). The anchored device is designed to continuously deliver the drug into the anterior chamber. Phase 3 trials began in 2018.

To complete this activity go to https://www.goteper.com/go/cb-glaucoma20 to access the online version of this activity and the posttest.

REFERENCES
Diagnosing LSCD noninvasively: SD-OCT preferred technology

Full-field option facilitates measurement of limbal crypt volume in patients

By Lynda Charters; Reviewed by Vincent M. Borderie, MD, PhD

Spectral-domain optical coherence tomography (SD-OCT) can be used to obtain highly detailed images of ocular tissues in vivo and in vivo assessments of both the corneal epithelium and limbal niche status.

Vincent M. Borderie, MD, PhD, showed the results he and colleagues have obtained using ex vivo full-field OCT when evaluating the morphology of the limbal niche. He discussed how complex the limbal niche structure is when observed using this technology.

“In assessing human donor corneas using full-field OCT, the limbal niche can be observed in 90% of normal human corneoscleral rims,” he said. “The limbal crypts extend between the palisades of Vogt and appear as radial in about 74% of cases and/or as rounded in 23% of cases.”

Dr. Borderie also noted that these structures often are interconnected by subconjunctival crypts in 56% of cases. He is professor of ophthalmology and chairman, Centre Hospitalier National d’Ophtalmologie des 15-20, Sorbonne University, Paris.

More crypts in humans are seen on the vertical meridian compared with the horizontal meridian.

Full-field OCT facilitates measurement of the limbal crypt volume. When the limbal stem cells are retrieved, they can be cultured at low density with mitomycin-arrested 3T3 feeders. With this protocol, he explained, the colony-forming efficiency can be demonstrated to increase with the limbal crypt volume.

“It makes sense to precisely analyze the limbal niche structure because it reflects the number of stem cells that are present in a given area,” Dr. Borderie said.

Dr. Borderie and his colleagues developed a protocol to assess LSCD in vivo using SD-OCT. They first look at the central cornea and then the limbal regions in the four quadrants and obtain cross sections parallel to the limbus, cross sections perpendicular to the limbus, and en-face sections.

Images of the central cornea in different eyes clearly show the differences between a normal cornea and one with advanced LSCD, in which the variability of the corneal epithelial thickness is much greater.

The investigators compared SD-OCT cross sections parallel to the limbus and used a scale of 0 to 3 to grade the findings in LSCD. Grade 0 indicated a cornea with advanced LSCD characterized by a flat hyporeflective stromal profile covered by a thin limbal epithelium and grade 3 indicated a normal cornea with clear, high, regular undulations of the limbal stromal surface forming ridges parallel to each other; in grade 3, the limbal niche is clearly visible with the palisades of Vogt and limbal crypts visible and even some buried limbal crypts, Dr. Borderie noted.

In SD-OCT cross sections perpendicular to the limbus, grade 2 indicates a normal cornea that is characterized by clear thickening with undulations over the entire ocular surface epithelium. In contrast, in grade 1, indicating advances LSCD, there is a completely flat profile.

In addition, in a normal cornea, the transition can be seen between the hyperreflective conjunctival epithelium and the hyporeflective corneal epithelium.

‘It makes sense to precisely analyze the limbal niche structure because it reflects the number of stem cells that are present in a given area.’

– Vincent Borderie, MD, PhD

In SD-OCT en-face sections of the limbal region, in a grade 2 normal cornea, the limbal niche is clearly visible with the palisades of Vogt and limbal crypts visible; in a grade 0 cornea with advanced LSCD, the features of the limbal niche are not visible.

Dr. Borderie and colleagues reported their results (American Journal of Ophthalmology. 2018;190:179-190).

**ANIRIDIA-ASSOCIATED KERATOPATHY**

Subepithelial fibrosis and LSCD are evident in this disease. The epithelial map showed the high variability of the corneal epithelial thickness. The SD-OCT cross sections showed that perpendicular and parallel to the limbus the profile was flat in all quadrants. The SD-OCT en-face sections no features of the limbal niche are visible. The diagnosis of aniridia-associated keratopathy was confirmed by in vivo confocal microscopy.

The study included 22 eyes with LSCD and 10 normal controls.

“In LSCD, the basement membrane and Bowman’s layer are lost in the vast majority of eyes and subepithelial fibrosis is present in 90% of cases,” Dr. Borderie said.

Evaluation of the limbus shows much lower scores in cases of LSCD. In the disease population, poorer visual acuity was significantly associated with the higher variability of the corneal epithelial thickness and lower limbal scores.

Dr. Borderie concluded that SD-OCT provides in vivo assessment of both the corneal epithelium and limbal niche status.

“The technologic advantage is that it provides a wide field of view and is a non-contact technique that permits detection of the limbal niche in eyes in which the condition of the ocular surface is poor,” he said. “The forthcoming development of in vivo full-field OCT will allow all information, that is, the information provided by in vivo confocal microscopy and SD-OCT, to be obtained with a single wide-field non-contact technology featuring cell resolution.”

**TAKE-HOME**

- Spectral-domain optical coherence tomography provides highly detailed images of limbal stem cell deficiency.
Technology ‘perfect’ for pediatric neuro-ophthalmology diagnoses

Optical coherence tomography offering fast, non-invasive option for physicians

By Lynda Charters; Reviewed by Mays A. El-Dairi, MD

**OPTICAL COHERENCE TOMOGRAPHY (OCT)** is popular for use in pediatric neuro-ophthalmology. The fast, non-invasive technology uses optical waves and interferometry, provides in vivo high-resolution tomograms, and displays pathologies that might otherwise go undetected.

“It is the ‘perfect’ non-invasive technology in pediatric neuro-ophthalmology patients with clear media,” said Mays A. El-Dairi, MD, associate professor, Pediatric Ophthalmology and Strabismus, Neuro-Ophthalmology, Duke Eye Center, Durham, NC.

In the pediatric population, OCT is used most frequently to obtain measurement of the retinal nerve fiber layer (RNFL). This is associated with a couple of drawbacks, she pointed out, one being that most machines do not have an integrated normative database.

In some cases, if there is one, the database is extrapolated and it is not highly accurate. The normative database needs to be perfected.

In her neuro-ophthalmology practice, Dr. El-Dairi puts the OCT instrument to use in many ways over and above just evaluating the RNFL. Many diseases can be diagnosed without OCT imaging, but the imaging provides information that might otherwise be impossible to obtain.

**VIEWING PEDIATRIC NEURO-OPTHALMIC DISEASE**

In patients with optic nerve hypoplasia, while OCT is not necessarily needed to establish a diagnosis most of the time, OCT facilitates measurement of the opening of Bruch’s membrane, which in optic nerve hypoplasia, is very small (Ophthalmology. 2015;122:1330-1339).

Optic nerve coloboma also can be diagnosed without use of OCT in most cases. However, in some cases when a tilted nerve is seen, a coloboma cannot always be identified as part of the optic nerve. OCT shows a signal that indicates that the nerve is just tilted, she explained.

In cases of optic nerve head pit, the end of Bruch’s membrane is not visible.

“OCT is not needed to see the pit, but sometimes the pit can be associated with an area where the ganglion cell area did not form, which can help predict a problem with visual function,” she said, describing a patient who had 20/200 vision and was undergoing treatment for amblyopia. In actuality, she was able to determine that the ganglion cells that facilitate central vision had never formed in this patient.

A myelinated nerve fiber layer seen on an OCT image has a bright, thick, hyperreflective signal that is readily visible. In some cases of subtle pseudopapilledema, visualization of this signal is helpful to the diagnosis.

In all congenital optic nerve anomalies, OCT allows clinicians to evaluate the central ganglion cell layer since it correlates with presence of a central scotoma when the patient is too young for a visual field evaluation, she said.

OCT is useful for examining Bruch’s membrane. When differentiating papilledema from pseudopapilledema, clinicians look for signs of high intracranial pressure and the position of Bruch’s membrane can provide clues.

“Upward bowing of the membrane can indicate the presence of a retrolubar process, something that is pushing behind the optic nerve, or high intracranial pressure,” Dr. El-Dairi said. “This is not a very sensitive marker, but it is quite specific; I always look at it when a nerve is elevated.”

The size of the Bruch’s membrane also can be evaluated using OCT. In patients with pseudopapilledema, the nerves tend to be smaller; the RNFL is under 120 μm and Bruch’s membrane opening is less than 1,500 μm. When compared with true papilledema, the pseudopapilledema nerves are larger; Bruch’s membrane opening exceeds 1,650 μm and the RNFL is thicker than 135 μm.

In optic neuritis, imaging shows RNFL thickening even when no edema is seen during fundoscopy. When optic atrophy becomes apparent, RNFL thinning is seen that is correlated with the final visual outcome.

“I imaging of the RNFL is not useful for diagnosing optic neuritis, but new baseline images are useful to have six months after resolution to more readily identify a recurrence,” she advised.

Dr. El-Dairi does, however, like to use OCT in children with optic neuritis because in some cases with a bright internal limiting membrane, early-stage neuroretinitis may not be apparent. Atrophic nerves are seen as thinning on the RNFL scan and macular map. Cystic lesions also may be visible in the inner nuclear layer.

“It is important to remember that when there is atrophy on top of papilledema, it is hard to determine how much is atrophy and how much is papilledema,” Dr. El-Dairi noted.

In a case of hydrocephalus, in which the patient had 20/400 vision, the RNFL measured about 80-μm and while the referring physician thought the patient was fine and had non-organic visual loss, the ganglion cell layer was actually absent.

Dr. El-Dairi relies on OCT to monitor the visual fields in young patients. In some cases, imaging will show changes at the macular level and homonymous thinning is seen that is correlated with visual field deficits.

In infants with nystagmus, she performs hand-held OCT evaluations to establish the need for electroretinography or neuroimaging.

Examples include Stargardt’s disease, retinoschisis, Best’s disease, and cone dystrophy, which have pathognomonic findings on the retinal OCT.

In an example of Leber congenital amaurosis, Dr. El-Dairi highlighted the normal ganglion cell layer and the significantly attenuated photoreceptor layer. She showed examples of different stages of retinitis pigmentosa that show only rod involvement initially that progresses to both rod and cone involvement.

Batten disease shows a very specific pattern on imaging—both the outer and inner retina are involved, there is severe attenuation of the ganglion cell layer, and the outer photoreceptors are significantly damaged.

“High-resolution OCT imaging tomograms of the retinal tissues can frequently reveal pathology that is difficult to detect with the naked eye,” Dr. El-Dairi concluded. “With extra anatomic finding, it can help determine the path for further workup.”

**TAKE-HOME**

› OCT uncovers pediatric retinal pathologies that are difficult to identify on examination.
Forty million people are blind worldwide, a staggering statistic. Broken down, 56% are affected by cataracts and uncorrected refractive errors, which can be handled easily with the available medical care. Other diseases, however, involve degenerative processes such as age-related macular degeneration (AMD) and pediatric blindness that are challenging because of the genetic causes.

Great strides have been made in identifying the offending genes, with 300 genes having been identified in association with the death of photoreceptors, retinal ganglion cells, or neurons in the retina, according to Paul A. Sieving, MD, PhD, professor of ophthalmology and founding director, Center for Ocular Regenerative Therapy, University of California Davis School of Medicine, Davis, CA, and previous director, National Eye Institute (NEI).

“Many of these conditions could be addressed with regenerative therapies,” Dr. Sieving said.

He predicted that the next two decades will see the emergence of potential treatments that can improve or restore vision, in contrast to the current treatments, i.e., intravitreal injections, laser photocoagulation, cryotherapy, and vitrectomy, that slow or ameliorate the disease process.

**TREATMENTS: INDIVIDUALIZED APPROACH**

Medicine is adopting a new focus. Physicians now are beginning to think initially about possible genetic factors involved in diseases.

The next step, according to Dr. Sieving, is to further develop the understanding of disease mechanisms at the cellular/tissue level.

This will bring physicians to the level of patient-specific clinical input to characterize the stage of disease progression for individual patients, he explained.

Intervention is subdivided into before cell loss with pharmacotherapy and gene therapies and during/after cell loss with restorative or replacement cell therapy and retinal prosthetics.

Therapeutics at both ends of the spectrum include the new rho kinase inhibitors for glaucoma, latanoprostene bunod ophthalmic solution 0.024% (Vyzulta, Bausch + Lomb) and netarsudil ophthalmic solution 0.02% (Rhopressa, Aerie Pharmaceuticals), comparison of anti-vascular endothelial growth factor drugs for AMD, and a retinal prostheses (Argus II, Second Sight).

**C E L L R E P L A C E M E N T T H E R A P Y**

The NEI adopted the ambitious project, the Audacious Goals Initiative (AGI) for Regenerative Medicine, in 2013, with the specific goal of regenerating neurons and neural connections in the eye and visual system—“all ideas that were beyond the current reach of our science and technology,” Dr. Sieving said.

This goal was immediately applicable to the loss of photoreceptor and retinal ganglion cells.

“The AGI is a 10- to 15-year effort to catalyze innovation and advance vision research to develop cells suitable for transfer to the retina, especially cells from the neuroprogenitor cell lines,” he said. “This will be done through the difficult processes of cell transplantation and cell integration into the host retina.”

There is a three-fold strategy to accomplish this that includes development of functional imaging technologies to explore cell function, identify novel neural regeneration factors that support the environment when cells are transplanted, and generate translation-enabling animal models that are appropriate for human disease and have ocular structures similar to humans.

Regarding the last, most recently nine awards have been funded, seven of which are for work with non-human primate models.

Adaptive optics is a technology that facilitates imaging of single retinal neurons. The technology allows evaluation of structural relationships between, for example, the photoreceptor cells and retinal pigment epithelium (RPE) or the movement of red blood cell flow through the capillaries, Dr. Sieving explained.

“The new imaging under development by the AGI will look at the function of those cells to evaluate metabolic activity using highly selective wavelengths to stimulate specific molecules in the retinoid cycle of the visual pigments,” Dr. Sieving said. “This will bring us closer to imaging actual cell dysfunction during disease progression and allow a closer look at therapeutic rescue.”

**ONGOING CELL THERAPY TRIALS**

The most recent newly funded trials include, for example, a single-center study to assess the safety and feasibility of cultivated autologous limbal epithelial cell transplantation for treating limbal stem cell deficiency conducted by Ula Jurkunas, MD, at Massachusetts Eye and Ear, Boston; a phase 1/II randomized, prospective cross-over study of intravitreal autologous bone marrow CD34+ stem cell therapy for retinal vein occlusion conducted by Suzanne Park, MD, PhD, at the University of California Davis; and induced pluripotent stem cell (iPSC)-derived RPE transplantation for dry AMD conducted by Kapil Bharti, PhD, at the NEI Intramural Research Program.

These studies are harvesting cells with stem cell-like properties to be used as human therapies.

In addition to the research supported by the NEI, Congress in 2016 established the 21st Century Cures Act that funded the National Institutes of Health (NIH) Regenerative Medicine Innovation Project (RMIP) with the stated goal of accelerating the regenerative medicine field by supporting clinical research on adult stem cells, including autologous stem cells. This act mandated coordination between the NIH and FDA to push forward the field of regenerative medicine.

The NIH has granted an award to study ABCB5+ stem cells for limbal stem cell deficiency conducted by Markus Frank, MD at Boston Children’s Hospital.

“There are major challenges ahead and risks for developing translational cell therapies.”

— Paul A. Sieving, MD, PhD
The RMIP also funded preclinical research that include study of precision genome surgery in autologous stem cell transplant to Stephen Tsang, MD, PhD, at Columbia University; preclinical testing of iPSC-derived RPE to treat macular degeneration to Alan Marmorstein, PhD, at Mayo Clinic Rochester; and transplantation of adult, tissue-specific RPE stem cells as therapy for non-exudative AMD to Jeff Stern, MD, PhD, at the Regenerative Research Foundation.

In addition to these, numerous studies are under way that are investigating RPE cell therapy for wet and dry AMD, Stargardt’s disease, retinitis pigmentosa, RPE tears, and Best disease, Dr. Sieving pointed out.

**GENE THERAPY**
In addition to the 40 million people who are blind worldwide, 285 million are visually impaired. The eye is especially well suited to gene therapy because it is a small compartment that facilitates targeted delivery of drugs, a small amount of vector is required, and there is a low risk of systemic toxicity. In addition, numerous animal models already have been established.

Voretigene neparvovec-rzyl (Luxtera, Novartis), is the first FDA-approved ocular gene therapy that is indicated for Leber congenital amaurosis and one of the first ever human diseases Dr. Sieving noted, to be treated by in vivo gene therapy.

“As ophthalmologists, we can now literally provide sight for the blind,” he noted.

There are currently more than 45 ongoing ocular gene therapy trials for inherited retinal dystrophies and new trial for AMD, making for an energetic clinical trial landscape, he said and explained that positive outcomes will be the basis for further advances.

Dr. Sieving is currently working on retinoschisis gene therapy; this genetic X-linked recessive disease affects 8,000 to 12,000 males in the United States. In this study, an AAV serotype 8 vector carrying the human RS1 gene, Thus far, 12 patients have been treated and the investigators have observed “a preliminarily potentially positive signal” indicating that the vector has entered the retina and closing the schisis cavities in one participant.

The still unanswered questions about gene therapy are inflammation and immune rejection, efficacy, best modes of vector delivery, and the durability of the effect.

According to Dr. Sieving, the future is bright for regenerative therapies for ocular disease. Clinicians expect some therapies to enter the clinic in the next 10 to 20 years.

“Our field is rich in innovation in ophthalmology and vision science, that is, visual cortical prostheses, nano-medicine, tissue engineering, drug and gene delivery systems, clinical endpoints, artificial intelligence, and disease modeling at the cellular level, and new clinical endpoints such as functional cellular imaging of retinal neurons,” he concluded.
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