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CUTTING-EDGE ADVANCEMENTS

November 1, 2014 VOL. 39, NO. 20

CLINICAL DIAGNOSIS | SURGERY | DRUG THERAPY

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Surgery

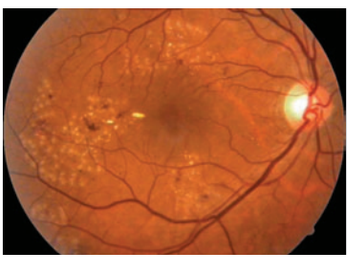
CATARACT SURGEONS 'TELL IT LIKE IT IS' IN UNIQUE FORMAT

SARASOTA, FL :: **WITH PLANNING** well under way for the fifth year of "Cataract Surgery: Telling It Like It Is!"—set for Jan. 15 to 18—meeting organizer and course director Robert H. Osher, MD, promises "more faculty, more topics, and a lot more fireworks" for this latest gathering. "We have re-engineered the program," he said.

*(See story on page 6 : **Cataract**)*

Special Report

LASER, INJECTION PARADIGMS FOR MACULAR EDEMA



GUJARAT, INDIA :: **WHEN** treating diabetic macular edema (DME), ophthalmologists often face the choice of which treatments—either alone or in combination—best prevent further damage to the retina, correct vision loss, and prevent eventual blindness, explained Manish Nagpal, MD.

*(See story on page 32 : **DME**)*

Drug-delivery micropump for chronic retina disorders

This controlled, refillable technology offers a feasible method to treat disease

By Michelle Dalton, ELS;
Reviewed by Mark S. Humayun, MD, PhD, and Julia A. Haller, MD

LOS ANGELES :: **THE "FIRST-IN-MAN"** implant of a novel ophthalmic drug delivery system (Posterior MicroPump, Replenish Inc.) in patients with diabetic macular edema (DME) demonstrates that use of the device "is feasible and warrants further development," according to Mark S. Humayun, MD, PhD.

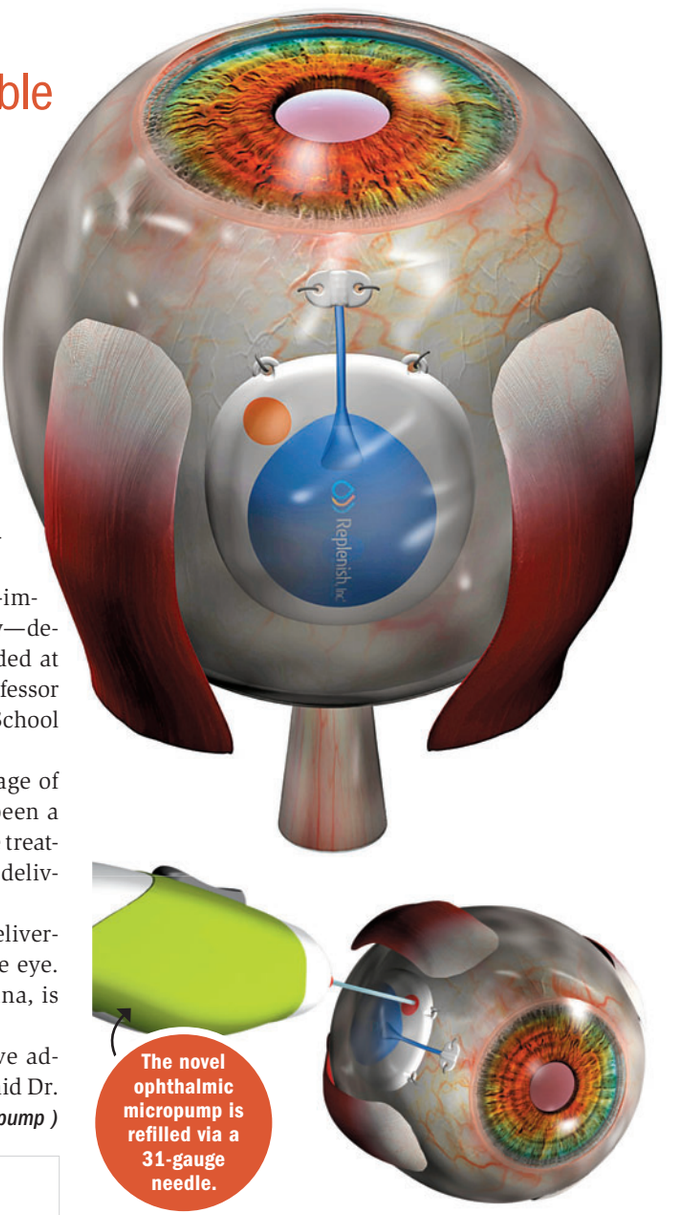
The small, refillable ocular drug pump—implanted through minimally invasive surgery—delivers the "appropriate amount of drug needed at determined intervals," said Dr. Humayun, professor of ophthalmology, USC Eye Institute, Keck School of Medicine, Los Angeles.

Localizing drug delivery has the advantage of avoiding systemic side effects, which has been a potential concern with current retinal disease treatments. Both suprachoroidal and intravitreal delivery may eliminate this issue altogether.

The pump provides the capabilities for delivering a programmable microdose direct to the eye. The cannula, inserted through the pars plana, is programmed wirelessly.

The device was initially designed to solve adherence issues for patients with glaucoma, said Dr.

*(Continues on page 42 : **Micropump**)*



IN VIEW: The pump can be programmed to dispense precise nanoliter-sized doses (a drug flow sensor gives closed-feedback) of drugs every hour, day, or month as needed over 6 to 9 months before the next refill. *(Images courtesy of Replenish Inc.)*

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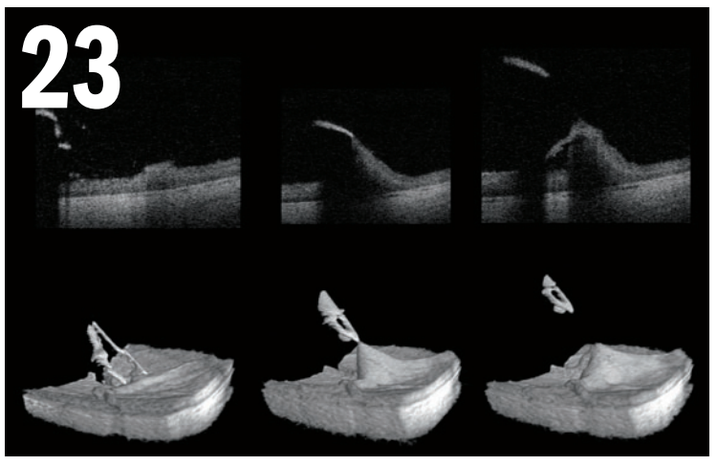

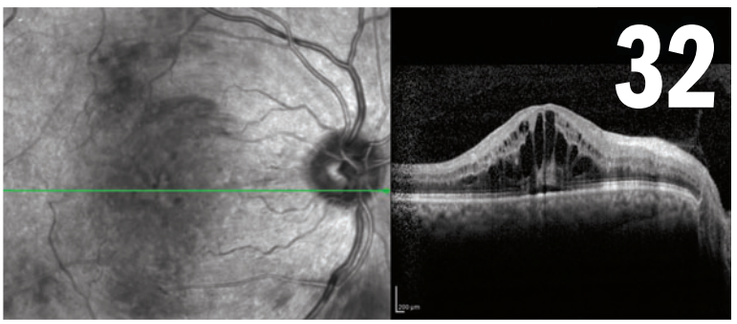

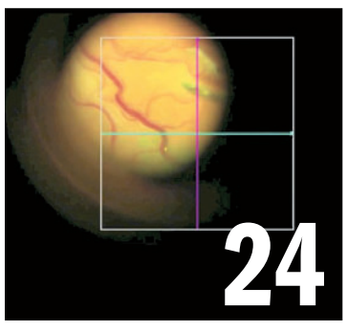

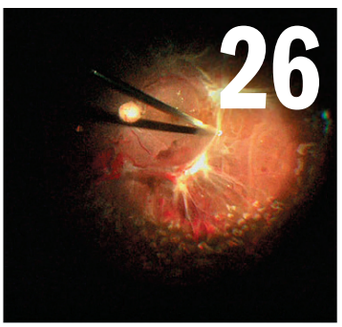

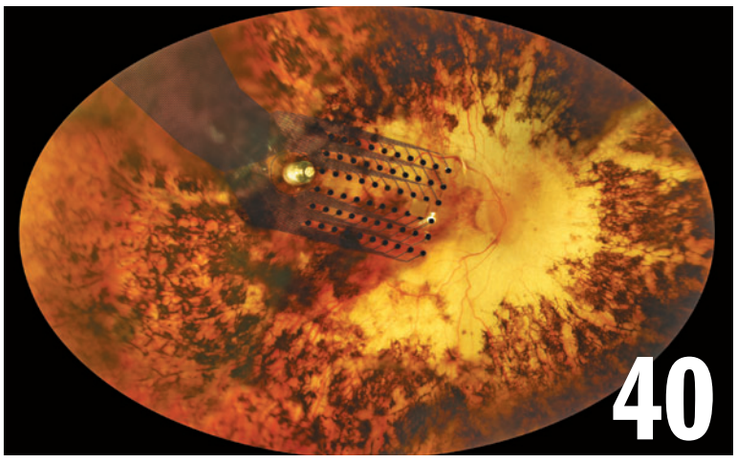

Surgery

Special Report

Drug Therapy

Technology

Clinical Diagnosis

Practice Management

The fullness of life

We physicians can get caught up in minutiae of medical practice

By Peter J. McDonnell, MD

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

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FIRST PERFORMED in 1938, the Thornton Wilder play "Our Town" received the Pulitzer Prize for Drama. The setting is a small town in New England, and instead of props, actors use pantomime to act out roles, like cooking imaginary meals in invisible kitchens and pretending to deliver bottles of milk from a transparent van drawn by a non-existent horse. As a result, our focus is entirely on the characters and their interactions, with everything orchestrated by a character known as "The Stage Manager."

In Act I, baseball star George Gibbs and pretty Emily Webb are two schoolmates who begin to feel affection for each other. George's mother, Julia, speaks about her dream of traveling to Paris.

In Act II, 3 years later, we learn that love has bloomed. George decides to forego college so he can marry Emily, become a farmer, and devote himself to being a responsible husband. George and Emily are married, excited about the life ahead of them.

In Act III, 9 years later, Emily, who has died in childbirth, is about to be buried. While her funeral service is conducted, Emily speaks with the dead souls who inhabit the cemetery. Among them is her mother-in-law, Julia, who never made it to Paris, having assumed there would be always be a time in the future to make the trip.

HOW FLEETING IS LIFE

Emily misses her life and—against the advice of the dead souls in the cemetery—decides to relive part of it. She steps back in time to the morning of her twelfth birthday, observing her young and beautiful parents. The experience is too painful for her, as she appreciates how fleeting is life and that it is not valued adequately by the living.

"Oh, earth," she laments, "you're too wonderful for anybody to realize you."

Emily returns to the cemetery where she settles in next to her deceased mother-in-law, while her husband George kneels and weeps.

Emily asks the Stage Manager if there are any humans who fully realize the fullness of life while they live it.

"No," he says. "The saints and poets, maybe—they do some."

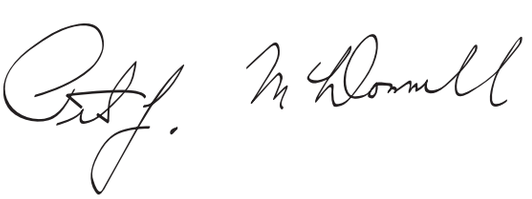
Only the audience members with the severest of dry eyes are not moistening up by the end of Act III. *The Christian Science Monitor* reported that in 1946 the Soviet Union banned the production of "Our Town" in the Russian sector of occupied Berlin "on the grounds that the drama is too depressing and could inspire a German suicide wave."

According to *The New York Times*, "Wilder makes a profound statement about the limits of human understanding here, one that requires delicacy and a little steel to convey. " 'Our Town' is one of the toughest, saddest plays ever written," Edward Albee has said.

STILL RELEVANT TODAY

This play may be three-quarters of a century old, but my feeling is that there is a message here for today's ophthalmologists. I sometimes think there is a risk that we physicians can get caught up in the minutiae of medical practice—transitioning to electronic medical records, fighting for pre-authorizations to get our patients the treatments they need, dealing with the Byzantine system of medical billing, etc.

As a result, we risk forgetting to experience fully the happiness that comes from helping the sick, the joy of restoring a person's vision, or the opportunity to show empathy and support for someone with a disease we cannot cure. ■



References

- Play 'Our Town' is Banned in Soviet Berlin Sector. *Christian Science Monitor,* Feb. 13, 1946, p. 13.
- *http://www.nytimes.com/2007/04/01/books/review/McCarter.t.html?_r=0*

Ophthalmology Times
NOVEMBER 1, 2014 ■ VOL. 39, NO. 20

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Cataract surgeons 'tell it like it is' for re-engineered 2015 meeting

Now in its 5th year, program provides intense, useful clinical information in innovative format

By Beth Thomas Hertz

SARASOTA, FL ::

With planning well under way for the fifth year of "Cataract Surgery: Telling It Like It Is!"—set for Thursday, Jan. 15, to Sunday, Jan. 18—meeting organizer and course director Robert H. Osher, MD, promises "more faculty, more topics, and a lot more fireworks" for this latest gathering here.

"We have re-engineered the program—adding many exciting new sessions," said Dr. Osher, professor of ophthalmology, University of Cincinnati, as well as medical director emeritus of the Cincinnati Eye Institute and editor of the *Video Journal of Cataract and Refractive Surgery*.

Dr. Osher

"We have added a lot more subspecialty updates—which are included in the registration fee—the day before the meeting and the morning it begins," he said.

These include sessions on retina, glaucoma, refractive surgery, cornea, and neuro-ophthalmology. "Wednesday Night at the Movies," hosted by Dr. Osher, will also be held the night before the meeting officially begins.

The keynote speech, "Uveitis and Cataract," will be given by Sunil Srivastava, MD—described by Dr. Osher as a charismatic and entertaining speaker—on Friday. The international guest speaker is Boris Malyugin, MD, of Moscow, Russia, whom Dr. Osher describes as a world-renowned innovator.

'Cataract Surgery: Telling It Like It Is!'

Thursday, Jan. 15 to Sunday, Jan. 18

The Ritz-Carlton Sarasota, FL

WHAT MAKES THE EVENT UNIQUE

The success of the meeting is due primarily to the uncensored information that is available and not restricted by continuing medical education (CME) guidelines. It also is affordable, has a top-notch faculty (See Page 9), and is at a Florida location that is more easily accessible than other popular winter meetings, he said.

"This meeting provides intense, useful clinical information in an innovative and entertaining format—unlike any other that you have ever attended," he said. "We want every attendee to depart Sarasota more confident about delivering the best possible surgical care."

Dr. Osher, who also is Associate Medical Editor on the Editorial Advisory Board for *Ophthalmology Times*, expects about 500 ophthalmologists this year—the most the venue can hold.

"This size still permits an intimate atmosphere with lots of audience interaction," he said.

The American Academy of Ophthalmology is organizing the logistics, he noted. About 90 exhibitors will attend as well—triple the number that attended the first meeting.

ATTENDEE DETAILS

The cost for residents and fellows is $300. For

Continues on page 9 : ***Telling It***

Schedule

For the latest program updates for this year's "Cataract Surgery: Telling It Like It Is!" meeting and for complete attendee registration details, visit *http://www.cstellingitlikeitis.com/*

THURSDAY, from 1 to 6 p.m., will be an "Afternoon of Technology." This event features side-by-side comparisons of technology: Phaco machine showdown, microscope showdown, presbyopia correction showdown, and femtosecond laser showdown. "Movie Madness," hosted by William Fishkind, MD, follows after dinner.

FRIDAY brings Intracameral Devices, Complications!, Case Dissections . . . Step-By-Step, and wet labs. These labs, for which attendees must pre-register, include intraoperative devices, anterior vitrectomy, trabectome, endocyclophotocoagulation, toric IOLs, topography, aberrometry, and optical coherence tomography interpretation. Later in the day there will be a 3-D video symposium, a session entitled "Strange But True!" and a late-night session with several faculty members.

SATURDAY brings hardcore vitrectomy, challenging cases, audience Q&A, small-pupil pptions, and a symposium on perioperative drugs. More wet labs will be held on Saturday afternoon, including advanced suturing, eye stents, YAG vitreolysis, ocular surface, iris reconstruction, and the Ophthalmic Mutual Insurance Co.'s Risk Management. Later in the day, there will be surgical guidance and toric IOLs, pre- and intraoperative aberrometry, MIGS, IOL exchange, Young Ophthalmologists' Forum "Ask Anything!," and "Saturday Night Live: Essential Practice Management" with John Pinto and Larry Patterson, MD.

SUNDAY The program wraps up by noon on Sunday after "Everyday Difficult IOL Decisions," "Take-Home-A-Pearl!", refractive surprises, and a final video session.

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ILEVRO® Suspension dosed once daily post-op has been shown to be noninferior to NEVANAC® (nepafenac ophthalmic suspension) 0.1% dosed three times daily for the resolution of inflammation and pain associated with cataract surgery.[2,3]

One drop of ILEVRO® Suspension should be applied once daily beginning 1 day prior to cataract surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery.[2]

Use of ILEVRO® Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.[2]

Available in 1.7 mL and new 3 mL fill sizes

INDICATIONS AND USAGE

ILEVRO® Suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- Increased Bleeding Time – With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use.

  Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- Contact Lens Wear – ILEVRO® Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO® Suspension, please refer to the brief summary of prescribing information on adjacent page.

References: 1. Formulary data provided by Pinsonault Associates, LLC, PathfinderRx, June 2014. **2.** ILEVRO® Suspension prescribing information. **3.** NEVANAC® Suspension prescribing information.

For more resources for eye care professionals, visit MYALCON.COM/ILEVRO

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO® Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO® Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO® Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Corneal Effects
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO® Suspension and should be closely monitored for corneal health. Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO® Suspension should not be administered while using contact lenses.

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

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO® Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO® Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO® Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO® Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO® Suspension in pediatric patients below the age of 10 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed in vitro to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes in vivo in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Contact Lens Wear
ILEVRO® Suspension should not be administered while wearing contact lenses.

Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Shake Well Before Use
Patients should be instructed to shake well before each use. U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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TELLING IT

(Continued from page 6)

practicing physicians, the cost is $600 by Dec. 17. Onsite registration, based on space availability, will be $650. Registration fees include general sessions, tutorials, exhibits, subspecialty updates, New Technology Symposium, sponsored breakfasts, and lunches. Wet labs have an additional fee.

Room blocks have been reserved at the Ritz-Carlton, Sarasota, the Hyatt Regency Sarasota, Hotel Indigo Sarasota, The Resort at Longboat Key Club, and The Lido Beach Resort.

The Ritz-Carlton, Sarasota
941/309-2000

Hyatt Regency Sarasota on Sarasota Bay
941/953-1234

Hotel Indigo Sarasota
877/834-3613

The Resort at Longboat Key Club
800/237-8821, ext. 7765

Lido Beach Resort
800/441-2113

The hotels are about 4 miles from the Sarasota/Bradenton International Airport, which is serviced by eight airlines. The Tampa International Airport has more flight options but is about 1 hour from the hotels.

The meeting is being held over the Martin Luther King Jr. holiday weekend. ■

Faculty

Though Robert H. Osher, MD, believes the program is excellent, the faculty is what brings attendees back each year. "They are all superb educators and leaders in their specialties," he said.

Ike Ahmed, MD, FRCSC, assistant professor, University of Toronto, Ontario, and clinical assistant professor, University of Utah, Salt Lake City

Lisa B. Arbisser, MD, ophthalmologist for Eye Surgeons Associates, Iowa and Illinois Quad Cities, and adjunct associate professor, University of Utah's John A. Moran Eye Center

Deepinder K. Dhaliwal, MD, associate professor of ophthalmology, University of Pittsburgh School of Medicine; director, Cornea Service and director Refractive Surgery Service, and director and founder, Center for Integrative Eye Care

William Fishkind, MD, FACS, clinical professor, University of Utah, Salt Lake City, and director, Fishkind, Bakeweel & Maltzman Eye Care and Surgery Center, Tucson, AZ

Bradley Fouraker, MD, Brandon Cataract Center and Eye Clinic, Brandon, FL, and St. Luke's Cataract and Intraocular Lens Institute, Tarpon Springs, FL, and Celebration, FL

Michael Hater, MD, Cincinnati Eye Institute and associate clinical professor of ophthalmology, University of Cincinnati College of Medicine

Warren Hill, MD, medical director, East Valley Ophthalmology, Mesa, AZ

Don Hood, MSc, PhD, James F. Bender Professor of Psychology and Professor of Ophthalmic Science, and Columbia University, New York

Anup K. Khatana, MD, director, Glaucoma Service and fellowship, Cincinnati Eye Institute, and volunteer clinical assistant professor of ophthalmology, University of Cincinnati College of Medicine

Richard Mackool, MD, director, Mackool Eye Institute and Laser Center, Astoria, NY

Boris Malyugin,MD, professor of ophthalmology, Department of Cataract and Implant Surgery, S. Fyodorov Eye Microsurgery Federal State Institution, Moscow

Steven A. Newman, MD, professor of ophthalmology, University of Virginia Health Systems

Jeffrey Odel, MD, professor of ophthalmology at Columbia University, New York

James Osher, MD, Cincinnati Eye Institute and assistant professor, University of Cincinnati College of Medicine

Larry Patterson, MD, medical director, Eye Centers of Tennessee and assistant clinical professor of ophthalmology, University of South Carolina

John Pinto, the most published author in the world on ophthalmic practice management and founder of J. Pinto & Associates, Inc., an ophthalmic practice management consulting firm

Christopher Riemann, MD, director, Vitreo-Retinal Fellowship, Cincinnati Eye Institute/University of Cincinnati and volunteer professor, University of Cincinnati

Michael Snyder, MD, voluntary assistant professor of ophthalmology, University of Cincinnati and in private practice at Cincinnati Eye Institute

Steven Vold, MD, founder of Vold Vision in Fayetteville and Bentonville, AR, chief medical editor of *Glaucoma Today*, and co-founder of the American-European Congress of Ophthalmic Surgery

Robert Weinstock, MD, director of cataract and refractive surgery, The Eye Institute of West Florida, Largo, FL, and assistant clinical professor, Department of Ophthalmology, University of South Florida, Tampa

Sonia Yoo, MD, professor of ophthalmology with a joint appointment in Biomedical Engineering and Associate Medical Director at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine

Richard Zorab, ONE Network founder, dies

By Rose Schneider

SAN FRANCISCO ::
RICHARD ZORAB, vice president for ophthalmic knowledge with the American Academy of Ophthalmology (AAO), has died at the age of 68.

Zorab built the academy's newly redesigned Ophthalmic News and Education (ONE) Network, an online source of peer-reviewed news and education for ophthalmologists.

He died shortly after receiving the Academy Guest of Honor Award during the organization's annual meeting last month in Chicago. He was the first education vice president in the academy's 118-year history to be honored with the award.

The Richard A. Zorab Memorial Fund has been established to support the ONE Network. Contributions may be made online at *http://bit.ly/1s8VaMr* or by mail to the Foundation of the American Academy of Ophthalmology, P.O. Box 7309, San Francisco, CA 94120-9833. For more information, e-mail *asoglin@aao.org.* ■

EK evolution: Accumulating data highlight the benefits of DMEK

Study supports DMEK as first choice of surgical therapy for routine Fuchs' dystrophy

By Cheryl Guttman Krader; *Reviewed by Mark A. Terry, MD*

PORTLAND, OR ::

A REVIEW OF the literature and outcomes of a new study comparing visual results of ultra-thin Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) in patients who had undergone both procedures support the conclusion that DMEK should be the first choice of surgical therapy for routine Fuchs' dystrophy or pseudophakic bullous keratopathy, said Mark A. Terry, MD.

"Ultra-thin DSAEK may be associated with better visual outcomes than DSAEK, but compared with ultra-thin DSAEK, we found that DMEK results in faster and better visual recovery as well as better quality of vision," said Dr. Terry, director of corneal services, Devers Eye Institute, Portland, OR. "Furthermore, in studies where patients have undergone DMEK in one eye and ultra-thin or standard DSAEK in the fellow eye, the majority of patients prefer the vision in the DMEK eye.

"However, DMEK is not an option for all eyes that are candidates for endothelial keratoplasty," he continued. "DMEK should not be performed in eyes that are aphakic or with pupils that cannot be constricted. Eyes with a trabeculectomy, glaucoma drainage tube, anterior chamber IOL that will be left in place, or prior vitrectomy are also not candidates for DMEK. Therefore, corneal surgeons doing DMEK need to keep their DSAEK skills sharp."

> 'DMEK results in faster and better visual recovery as well as better quality of vision.'
>
> — Mark A. Terry, MD

Reviewing the evolution of EK from deep lamellar EK to DMEK, Dr. Terry noted that the average vision level and quality of vision achieved improved with each new method that was introduced. Improvement in the interface between the donor and the recipient explains this trend. Although DSAEK was the first procedure juxtaposing smooth stroma to smooth stroma, DMEK represents a further advance because it eliminates donor stroma to provide an exact anatomic replacement.

EXAMINING THE EVIDENCE

Results of a study by Price et al. published in 2011 [*Cornea.* 2011;30:1382-1386] showed superior visual outcomes after DMEK compared with standard thickness DSAEK (attempted graft thickness 120 µm). In that investigation that included 15 patients who had one of each procedure and were followed to 1 year, mean best-corrected visual acuity (BCVA) was 20/24 for DMEK eyes and 20/32 for DSAEK eyes.

Compared with DSAEK, DMEK was also associated with a higher rate of 20/20 or better BCVA (38% versus 8%) and a higher proportion of patients who would recommend the procedure to others (62% versus 15%).

The benefit of ultra-thin DSAEK for providing better visual acuity outcomes than standard thickness DSAEK was demonstrated in a paper by Busin et al. [*Ophthalmology.* 2013;120:1186-1194]. In that study, which included 285 eyes, 26% achieved 20/20 or better BCVA after 6 months.

Dr. Terry and colleagues undertook an analysis to compare the outcomes of DMEK and ultra-thin DSAEK in patients who had undergone the two procedures in fellow eyes. The study included 21 patients. Mean preoperative BCVA was similar in the DMEK and ultra-thin DSAEK eyes.

However, at 6 months postoperative, mean BCVA was better in the DMEK eyes than in the ultra-thin DSAEK eyes (20/24 versus 20/28), and a higher proportion of DMEK eyes was seeing 20/20 or better (45% versus 18%).

Nineteen patients were questioned about whether they preferred one eye to the other because of better vision, and 14 (74%) of those patients favored their DMEK eye. One patient (5%) felt vision was similar in both eyes while 4 (21%) patients preferred the vision in their DSAEK eye.

TAKE-HOME

- ***Descemet membrane endothelial keratoplasty results in better vision and better quality of vision than standard or ultra-thin Descemet stripping automated endothelial keratoplasty.***

FURTHER STUDIES

In a separate study, Dr. Terry and colleagues analyzed higher-order aberrations after DMEK and ultra-thin DSAEK using Scheimpflug imaging (Pentacam, Oculus).

The study included 33 eyes that had DMEK, 30 post-DSAEK eyes, and 30 controls. The results showed that total posterior cornea aberrations were significantly higher in eyes that had DSAEK compared with DMEK eyes (0.43 versus 0.25 root mean square; $p = 0.0005$), but there was no difference comparing DMEK eyes with controls (0.25 root mean square for both).

Analysis of posterior spherical aberration showed a trend toward lower aberration in the DMEK eyes compared with the DSAEK group (0.17 versus 0.23 root mean square; $p = 0.07$), while mean posterior spherical aberration was identical in the DMEK eyes and the control group.

"Better quality of vision after DMEK compared with DSAEK is likely due to the elimination of posterior irregularities resulting in less higher-order aberrations," Dr. Terry said. ■

MARK A. TERRY, MD

E: *mterry@deverseye.org*

This article was adapted from Dr. Terry's presentation at the 2014 meeting of the American Society of Cataract and Refractive Surgery. Dr. Terry has no relevant financial disclosures for this presentation.

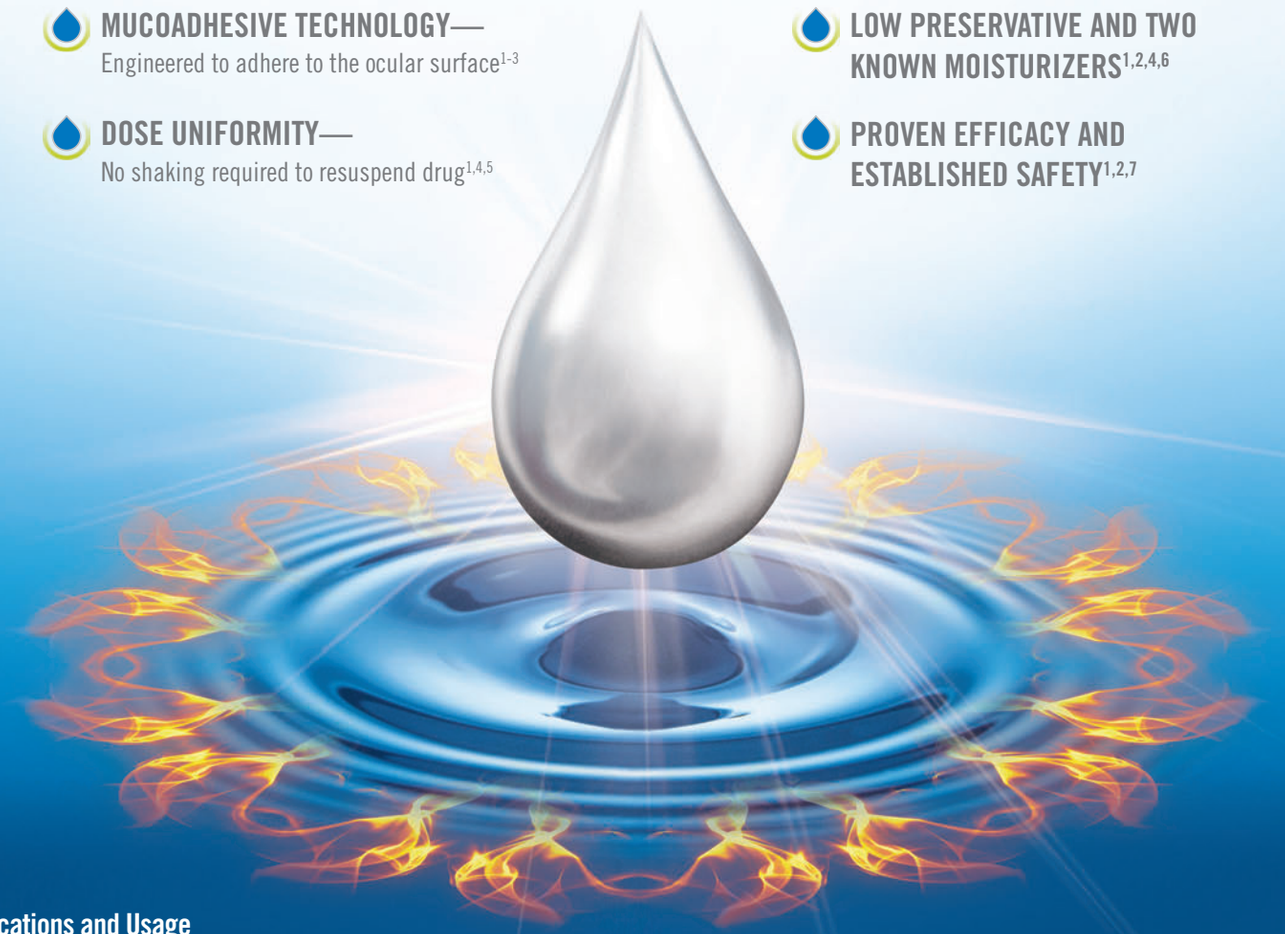
LOTEMAX® GEL—UNIQUE FORMULATION DESIGNED TO CONTROL INFLAMMATION

MUCOADHESIVE TECHNOLOGY—
Engineered to adhere to the ocular surface[1-3]

DOSE UNIFORMITY—
No shaking required to resuspend drug[1,4,5]

LOW PRESERVATIVE AND TWO KNOWN MOISTURIZERS[1,2,4,6]

PROVEN EFFICACY AND ESTABLISHED SAFETY[1,2,7]



Indications and Usage

- LOTEMAX® GEL is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery

Important Risk Information about LOTEMAX® GEL

- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures
- Intraocular pressure (IOP) increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored
- Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation
- Delayed healing—Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification
- Bacterial infections—Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infections
- Viral infections—Use of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex)
- Fungal infections—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use
- Contact lens wear—Patients should not wear contact lenses when using LOTEMAX® GEL
- The most common ocular adverse drug reactions were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%)

Please see brief summary of full prescribing information on adjacent page.

References: 1. LOTEMAX GEL Prescribing Information, September 2012. **2.** Fong R, Leitritz M, Siou-Mermet R, Erb T. Loteprednol etabonate gel 0.5% for postoperative pain and inflammation after cataract surgery: results of a multicenter trial. *Clin Ophthalmol.* 2012;6:1113-1124. **3.** Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J Pharm Bioallied Sci.* 2011;3(1):89-100. **4.** Data on file, Bausch & Lomb Incorporated. **5.** Coffey MJ, Davio SR. Viscoelastic and sedimentation characterization of loteprednol etabonate ophthalmic gel, 0.5%. Poster presented at: Association for Research in Vision and Ophthalmology (ARVO); May 6-10, 2012; Fort Lauderdale, FL. Poster #6283/D1143. **6.** Lotemax Prescribing Information, April 2006. **7.** Rajpal RK, Roel I, Siou-Mermet R, Erb T. Efficacy and safety of loteprednol etabonate 0.5% gel in the treatment of ocular inflammation and pain after cataract surgery. *J Cataract Refract Surg.* 2013;39:158-167.

BAUSCH+LOMB

LOTEMAX® GEL
loteprednol etabonate ophthalmic gel 0.5%
DISCOVER THE POWER OF GEL

BAUSCH + LOMB

LOTEMAX®

loteprednol etabonate
ophthalmic gel 0.5%

Brief Summary: Based on full prescribing information.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

FOR MORE DETAILED INFORMATION, PLEASE READ THE PRESCRIBING INFORMATION.

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA
US Patent No. 5,800,807

Study: Diabetes drug could reduce the risk of open-angle glaucoma

Effect of caloric restriction-mimetic medication may benefit other age-related eye diseases

By Vanessa Caceres; *Reviewed by Julia E. Richards, PhD*

ANN ARBOR, MI ::

A drug used for patients with diabetes could one day become an additional therapy to reduce the risk of open-angle glaucoma (OAG).

Researchers tested this hypothesis by analyzing 10 years (2001 to 2010) of longitudinal data from a large, U.S. health-claims database, according to Julia E. Richards, PhD.

They monitored patients above the age of 40 years with diabetes and who had no pre-existing OAG. They also determined whether the patients used the medication metformin.

TAKE-HOME

- ***Use of metformin, a drug therapy for the treatment of diabetes, was found to be associated with reduced risk of adult-onset, open-angle glaucoma in a recent study.***

The study fits into the broader area of aging research and the use of caloric restriction medications, according to Dr. Richards, Harold F. Falls Professor of Ophthalmology and Visual Sciences, professor of epidemiology, and director of the Glaucoma Research Center, University of Michigan, Ann Arbor, MI.

"It has long been known that caloric restriction through use of a reduced-calorie diet can extend lifespan," she said. "Further exploration of this topic has shown that there are medications called caloric restriction-mimetic medications; because they imitate or mimic effects of calorie restriction, they can also extend lifespan. Metformin is one of these caloric mimetic medications."

Other studies have shown how these kinds of medications are associated with reduced risk for later-onset diseases, like some cancers, diabetes, and cardiovascular diseases, according to Dr. Richards.

"Because primary open-angle glaucoma is a late-onset disease, we hypothesized that a caloric restriction mimetic drug might be able to reduce the risk of glaucoma and that the risk reduction might involve action through one or more of these same aging pathways," she explained.

RESEARCH RESULTS

Researchers tested the effect of metformin on the risk of developing OAG, adjusting for sociodemographic factors, glycemic control via HbA1c levels, other diabetes medications, and other ocular and systemic conditions.

Of the 150,016 diabetics included in the study, 3.9% developed incident OAG. However, use of more than 1,110 cumulative grams of metformin over 2 years was associated with a 25% reduction in relative risk of developing OAG compared with no metformin use.

"Every 1 gram increase in metformin was associated with a 0.01% reduced hazard of developing OAG," the researchers reported.

"For example," they said, "a person receiving a 2-g daily dose of metformin—considered a normal dose—over 2 years would show a 13% reduction in absolute risk of OAG relative to someone who did not use the medication."

Even when researchers took into account HbA1c levels to monitor blood glucose, the reduction in risk still occurred.

"Also, the other medications used to control diabetes were not associated with reduced risk of OAG," Dr. Richards said.

MECHANISM OF ACTION

Dr. Richards suggested that this finding might shed light on the mechanism by which glaucoma risk is reduced.

"Metformin may be acting through one of the caloric restriction-mimetic mechanisms, such as pathways involving inflammation, neurogenesis, or one of the aging pathways," Dr. Richards said. "It's not clear yet if the same findings apply to other types of glaucoma, although that would be useful to know for future research."

It's also not yet known if metformin can be used to reduce the risk of OAG in non-diabetic patients, she added.

Future work done by Dr. Richards and fellow researchers may explore how metformin affects the risk of glaucoma development in other forms of glaucoma.

They also will explore which tissues in the eye change gene expression in response to metformin and investigate whether metformin can reduce the risk of other age-related eye diseases.

> 'Eventually, the already FDA-approved metformin medication might become available as an additional therapeutic approach to glaucoma.' *– Julia E. Richards, PhD*

Ultimately, metformin could be added the armamentarium for glaucoma treatment, she noted.

"Eventually, the already FDA-approved metformin medication might become available as an additional therapeutic approach to glaucoma," Dr. Richards said. ■

JULIA E. RICHARDS, PHD

E: *richj@umich.edu*

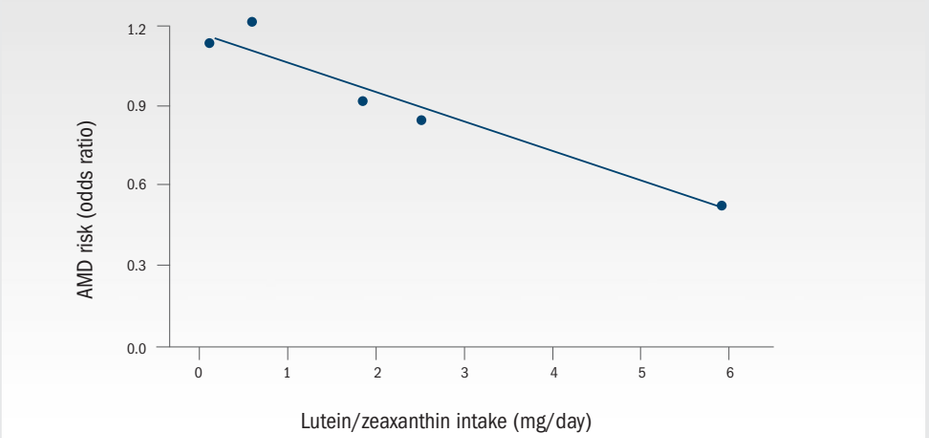
This article was adapted from Dr. Richard's presentation at the 2014 meeting of the Association for Research in Vision and Ophthalmology. Dr. Richards did not indicate any proprietary interest in the subject matter.

Lutein, zeaxanthin assist in visual function both early, later in life

Research finds benefits for AMD prevention; may improve infant visual performance

By Vanessa Caceres; *Reviewed by Paul S. Bernstein, MD, PhD*

Lutein and Zeaxanthin Intake and AMD Risk



This graph illustrates a 57% risk reduction with 6-mg lutein intake as compared with 1 mg.
Source: Seddon et al. *JAMA.* 1994;272:1413-1420. *(Figure courtesy of Paul S. Bernstein, MD, PhD)*

Why Study Macular Pigment in Infants and Children?

- Diseases of aging, such as AMD, may depend on light and oxidative stress that accumulates over a lifetime, including childhood.
- The macular pigment may exert a beneficial influence on foveal and visual development or vice versa (albinos have a hypoplastic fovea and no macular pigment).
- The macular carotenoids might modulate risk of ROP through antioxidant effects. ■

SALT LAKE CITY ::

THE MACULAR PIGMENT carotenoids lutein and zeaxanthin are well known within ocular nutrition for their role in protecting against age-related macular degeneration (AMD).

However, their power to assist with visual function may go beyond just AMD, said Paul S. Bernstein, MD, PhD, Mary Boesche Professor of Ophthalmology and Visual Sciences, John A. Moran Eye Center, University of Utah, Salt Lake City.

Lutein and zeaxanthin are two of 600 carotenoids found in nature. However, there are only 50 that humans consume, and just 10 to 15 that are absorbed, Dr. Bernstein said.

"Lutein and zeaxanthin are the only two carotenoids found in the retina itself," he said.

Lutein is found in dark green and leafy vegetables like kale and spinach as well as in egg yolks. Zeaxanthin is found in orange and yellow fruits and vegetables like corn and orange peppers as well as in egg yolks.

The value of lutein and zeaxanthin in the quest to protect against AMD led Age-Related Eye Disease Study 2 (AREDS2) researchers to test the addition of 10 mg of lutein and 2 mg of zeaxanthin to the original AREDS formula as a substitute for beta carotene.[1]

It was thought that the two carotenoids would be safe and effective substitutes for beta carotene, Dr. Bernstein said, referring to concerns of putting users, particularly smokers, at higher risk for lung cancer from the high beta carotene concentration in the original AREDS supplement.

Now, Dr. Bernstein and colleagues are turning their attention to the importance of lutein and zeaxanthin in early life, specifically how supplementation with the two carotenoids may help with visual acuity and foveal development. He and fellow researchers have developed a way to measure their presence in babies after birth by viewing the infant macular pigment with use of an imaging system (RetCam, Clarity Medical Systems).[2]

"We did a study in 2013 where we showed how macular pigment was detectable shortly after birth and develops through age 7," Dr. Bernstein said. "Yet, premature babies don't have any macular pigment at all."[3]

This research may help provide future clues to the role of macular carotenoids in modulating the risk of retinopathy of prematurity, according to Dr. Bernstein.

A related study conducted by Dr. Bernstein and colleagues focused on 14 full-term newborn infants and their mothers, during which serum carotenoids of the mother and child were measured by high-pressure liquid chromatography, and macular pigment imaging took place with the imaging system.[4]

TAKE-HOME

- ***A diet that contains lutein and zeaxanthin—or supplementation with these two carotenoids—appears to benefit healthy vision throughout life, explains Paul S. Bernstein, MD, PhD.***

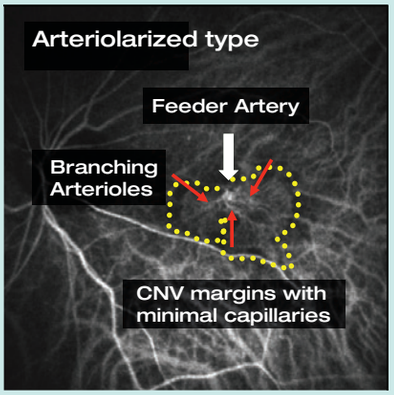
Continues on page 17 : ***Visual function***

In wet AMD patients with predominantly classic lesions...

Visudyne®
verteporfin for injection

Can induce vaso-occlusion of the arteriolarized neovessels that may be the cause of persistent activity[1-5]

- Arteriolarized-type of neovascular AMD is not VEGF-mediated and may need vaso-occlusive therapy[1-5]
- With branching arteriolarized vascular complex (AVC), lesions can increase in size while undergoing treatment with an anti-VEGF[1-2,4]
- **Evidence of neovessel remodeling and large caliber, branching AVC are reasons to select PDT for treatment[1,4]**



ICGA image courtesy of Scott Cousins, MD[1]

Make Visudyne® a part of your treatment loop

Indications and Usage

Visudyne® (verteporfin for injection) is indicated for the treatment of predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis.

There is insufficient evidence to indicate Visudyne® for the treatment of predominantly occult subfoveal choroidal neovascularization.

Important Safety Information

- Visudyne® (verteporfin for injection) is contraindicated for patients with porphyria or known hypersensitivity to any of its components.
- Avoid exposure of skin and eyes to direct sunlight or bright indoor light for 5 days. If extravasation occurs during infusion, the extravasation area must be thoroughly protected from direct light until swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.
- Patients who experience severe vision decrease (≥4 lines within 1 week) should not be retreated until their vision completely recovers to pretreatment levels and potential benefits and risks of subsequent treatment are carefully considered.
- Use of incompatible lasers that do not provide the required characteristics of light for photoactivation of Visudyne® could result in incomplete treatment due to partial photoactivation or overtreatment due to overactivation, or damage to surrounding normal tissue.
- For injection of Visudyne®, avoid small hand veins in favor of the largest possible arm vein, preferably the antecubital vein.
- The most frequently reported adverse events (10% to 30% incidence) were injection site reactions (including pain, edema, inflammation, extravasation, rashes, hemorrhage, and discoloration), and visual disturbances (including blurred vision, flashes of light, decreased visual acuity, and visual field defects, including scotoma).

Please see Brief Summary of Prescribing Information on adjacent page.

References: 1. Cousins et al, unpublished, presented at Royal Hawaiian Eye, 2014. **2.** Cho M, Barbazetto IA, Freund KB. Refractory neovascular age-related macular degeneration secondary to polypoidal choroidal vasculopathy. *Am J Ophthalmol.* 2009;148(1):70-78. **3.** Schmidt-Erfurth U, Kriechbaum K, Oldag A. Three-Dimensional Angiography of Classic and Occult Lesion Types in Choroidal Neovascularization. *IOVS* 2007;48(4):1751-1760. **4.** Cousins SW. Controversies in Long-term AMD Management. Retinal Physician website. http://www.retinalphysician.com/articleviewer.aspx?articleID=103843. Published January 2010. Accessed March 20, 2014 **5.** Bressler NM. Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin:two-year results of 2 randomized clinical trials—TAP report 2. *Arch Ophthalmol.* 2001;119(2):198-207.

US/VID/14/0009a

Visudyne®

(verteporfin for injection)

Rx only

BRIEF SUMMARY: Please see package insert for full Prescribing Information

INDICATIONS AND USAGE

Visudyne® (verteporfin for injection) therapy is indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.

There is insufficient evidence to indicate Visudyne for the treatment of predominantly occult subfoveal choroidal neovascularization.

CONTRAINDICATIONS

Visudyne® (verteporfin for injection) is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation.

WARNINGS

Following injection with Visudyne® (verteporfin for injection), care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

Patients who experience severe decrease of vision of ≥4 lines within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Use of incompatible lasers that do not provide the required characteristics of light for the photoactivation of Visudyne could result in the incomplete treatment due to partial photoactiviation of Visudyne, overtreatment due to overactivation of Visudyne, or damage to surrounding normal tissue.

PRECAUTIONS

General

Standard precautions should be taken during infusion of Visudyne® (verteporfin for injection) to avoid extravasation. Examples of standard precautions include, but are not limited to:

- A free-flowing intravenous (IV) line should be established before starting Visudyne infusion and the line should be carefully monitored.
- Due to the possible fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection.
- Small veins in the back of the hand should be avoided.

Extravasation of Visudyne, especially if the affected area is exposed to light, can cause severe pain, inflammation, swelling or discoloration at the injection site.

If extravasation does occur, the infusion should be stopped immediately. The extravasation area must be thoroughly protected from direct light until swelling and discoloration have faded in order to prevent the occurrence of a local burn, which could be severe. Cold compresses should be applied to the injection site (see WARNINGS). Oral medications for pain relief may be administered.

Visudyne therapy should be considered carefully in patients with moderate to severe hepatic impairment or biliary obstruction since there is no clinical experience with verteporfin in such patients.

There is no clinical data related to the use of Visudyne in anesthetized patients. At a >10-fold higher dose given by bolus injection to sedated or anesthetized pigs, verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious, nonsedated pigs. Visudyne resulted in a concentration-dependent increase in complement activation in human blood in vitro. At 10 µg/mL (approximately 5 times the expected plasma concentration in human patients), there was mild to moderate complement activation. At ≥100 µg/mL, there was significant complement activation. Signs (chest pain, syncope, dyspnea, and flushing) consistent with complement activation have been observed in <1% of patients administered Visudyne. Patients should be supervised during Visudyne infusion.

Information for Patients

Patients who receive Visudyne will become temporarily photosensitive after the infusion. Patients should wear a wristband to remind them to avoid direct sunlight for 5 days. During that period, patients should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light. Sources of bright light include, but are not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental offices. Prolonged exposure to light from light-emitting medical devices such as pulse oximeters should also be avoided for 5 days following Visudyne administration.

If treated patients must go outdoors in daylight during the first 5 days after treatment, they should protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light.

Patients should not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

Following Visudyne treatment, patients may develop visual disturbances such as abnormal vision, vision decrease, or visual field defects that may interfere with their ability to drive or use machines. Patients should not drive or use machines as long as these symptoms persist.

Drug Interactions

Drug interaction studies in humans have not been conducted with Visudyne.

Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolism is limited and occurs by liver and plasma esterases. Microsomal cytochrome P450 does not appear to play a role in verteporfin metabolism.

Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of Visudyne therapy. Possible examples include the following:

Calcium channel blockers, polymyxin B or radiation therapy could enhance the rate of Visudyne uptake by the vascular endothelium. Other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics and griseofulvin) could increase the potential for skin photosensitivity reactions. Compounds that quench active oxygen species or scavenge radicals, such as dimethy sulfoxide, β-carotene, ethanol, formate and mannitol, would be expected to decrease Visudyne activity. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could also decrease the efficacy of Visudyne therapy.

Carcinogenesis, Mutagensis, Impairment of Fertility

No studies have been conducted to evaluate the carcinogenic potential of verteporfin.

Photodynamic therapy (PDT) as a class has been reported to result in DNA damage including DNA strand breaks, alkali-labile sites, DNA degradation, and DNA-protein cross links which may result in chromosomal aberrations, sister chromatid exchanges (SCE), and mutations. In addition, other photodynamic therapeutic agents have been shown to increase the incidence of SCE in Chinese hamster ovary (CHO) cells irradiated with visible light and in Chinese hamster lung fibroblasts irradiated with near UV light, increase mutations and DNA-protein cross-linking in mouse L5178 cells, and increase DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Verteporfin was not evaluated in these latter systems. It is not known how the potential for DNA damage with PDT agents translates into human risk.

No effect on male or female fertility has been observed in rats following intravenous administration of verteporfin for injection up to 10 mg/kg/day (approximately 60- and 40-fold the human exposure at 6 mg/m^2 based on AUC_{inf} in male and female rats, respectively).

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Rat fetuses of dams administered verteporfin for injection intravenously at ≥10 mg/kg/day during organogenesis (approximately 40-fold the human exposure at 6 mg/m^2 based on AUC_{inf} in female rats) exhibited an increase in the incidence of anophthalmia/microphthalmia. Rat fetuses of dams administered 25 mg/kg/day (approximately 125-fold the human exposure at 6 mg/m2 based on AUC_{inf} in female rats) had an increased incidence of wavy ribs and anophthalmia/microphthalmia.

In pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received verteporfin for injection intravenously at ≥10 mg/kg/day during organogenesis. The no observed adverse effect level (NOAEL) for maternal toxicity was 3 mg/kg/day (approximately 7-fold the human exposure at 6 mg/m^2 based on body surface area). There were no teratogenic effects observed in rabbits at doses up to 10 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Visudyne should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Nursing Mothers

Verteporfin and its diacid metabolite have been found in the breast milk of one woman after a 6 mg/m^2 infusion. The verteporfin breast milk levels were up to 66% of the corresponding plasma levels and declined below the limit of quantification (2 ng/mL) within 24 hours. The diacid metabolite had lower peak concentrations but persisted up to at least 48 hours.

Because of the potential for serious adverse reactions in nursing infants from Visudyne, a decision should be made whether to discontinue nursing or postpone treatment, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Approximately 90% of patients treated with Visudyne in the clinical efficacy trials were over the age 65. A reduced treatment effect was seen with increasing age.

ADVERSE REACTIONS

Severe chest pain, vasovagal and hypersensitivity reactions have been reported. Vasovagal and hypersensitivity reaction on rare occasions can be severe. These reactions may include syncope, sweating, dizziness, rash, dyspnea, flushing and changes in blood pressure and heart rate. General symptoms can include headache, malaise, urticaria, and pruritus.

The most frequently reported adverse events to Visudyne® (verteporfin for injection) are injection site reactions (including pain, edema, inflammation, extravasation, rashes, hemorrhage, and discoloration) and visual disturbances (including blurred vision, flashes of light, decreased visual acuity and visual field defects, including scotoma). These events occurred in approximately 10%-30% of patients. The following events, listed by Body System, were reported more frequently with Visudyne therapy than with placebo therapy and occurred in 1%-10% of patients:

Ocular Treatment Site: Blepharitis, cataracts, conjunctivitis/conjunctival injection, dry eyes, ocular itching, severe vision decrease with or without subretinal/retinal or vitreous hemorrhage
Body as a Whole: Asthenia, fever, flu syndrome, infusion-related pain primarily presenting as back pain, photosensitivity
reactions
Cardiovascular: Atrial fibrillation, hypertension, peripheral vascular disorder, vericose veins
Dermatologic: Eczema
Digestive: Constipation, gastrointestinal cancers, nausea
Hemic and Lymphatic: Anemia, white blood cell count decreased, white blood cell count increased
Hepatic: Elevated liver function tests
Metabolic/Nutritional: Albuminuria, creatinine increased
Musculoskeletal: Arthralgia, arthrosis, myasthenia
Nervous System: Hypesthesia, sleep disorder, vertigo
Respiratory: Cough, pharyngitis, pneumonia
Special Senses: Cataracts, decreased hearing, diplopia, lacrimation disorder
Urogenital: Prostatic disorder

Severe vision decrease, equivalent of ≥4 lines, within 7 days after treatment has been reported in 1%-5% of patients. Partial recovery of vision was observed in some patients. Photosensitivity reaction usually occurred in the form of skin sunburn following exposure to sunlight. The higher incidence of back pain in the Visudyne group occurred primarily during infusion.

The following adverse events have occurred either at low incidence (<1%) during clinical trials or have been reported during the use of Visudyne in clinical practice where these events were reported voluntarily from a population of unknown size and frequency of occurrence cannot be determined precisely. They have been chosen for inclusion based on factors such as seriousness, frequency of reporting, possible causal connection to Visudyne, or a combination of these factors:

Ocular Treatment Site: Retinal detachment (nonrhegmatogenous), retinal or choroidal vessel nonperfusion, retinal pigment epithelial tear
Nonocular Events: Chest pain and other musculoskeletal pain during infusion

OVERDOSAGE

Overdose of drug and/or light in the treated eye may result in nonperfusion of normal retinal vessels with the possibility of severe decrease in vision that could be permanent. An overdose of drug will also result in the prolongation of the period during which the patient remains photosensitive to bright light. In such cases, it is recommended to extend the photosensitivity precautions for a time proportional to the overdosage.

QLT3188 Rev. 09/13
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Role of steroids in bacterial keratitis further defined; guides patient care

NEI-sponsored study provides some reassuring data on the controversial topic

By Cheryl Guttman Krader; *Reviewed by Bennie H. Jeng, MD, MS*

BALTIMORE ::

THE STEROIDS FOR Corneal Ulcers Trial (SCUT) is an important study that provides high-level scientific evidence to guide care of patients with bacterial corneal ulcers, said Bennie H. Jeng, MD, MS.

Dr. Jeng

Based on the results of SCUT, ophthalmologists can feel more comfortable using topical corticosteroids as an adjunct to antibiotics to treat a bacterial corneal ulcer in many circumstances, assuming there is no impending or present perforation, he noted.

In addition, the study data suggest starting the steroid earlier after diagnosis, within 2 or 3 days, may be better than delaying its initiation.

"SCUT is not without its limitations," said Dr. Jeng, professor and chairman, Department of Ophthalmology and Visual Sciences, University of Maryland School of Medicine, Baltimore. "However, it was a rigorously designed well-powered study. While it did not show any obvious benefit of steroid use as an adjunct to a topical antibiotic regarding the primary endpoint, it also found no serious safety concerns.

"Keeping in mind that clinical judgment is always needed because every corneal ulcer is different, SCUT is a valuable study because it allays some long-standing fears about the use of steroids in eyes with bacterial keratitis," he said.

Although theoretically, steroid treatment could improve visual outcomes by controlling inflammation that could lead to tissue destruction and scarring, there has long been concern surrounding steroid use due to the potential for delayed epithelial healing and worsening of the infection, particularly when *Pseudomonas aeruginosa* is the pathogen.

However, as stated in the American Academy of Ophthalmology's Preferred Practice Pattern Guidelines on bacterial keratitis version available prior to SCUT, "there is insufficient evidence to make an official recommendation."

Sponsored by the National Eye Institute, SCUT was a randomized, double-masked, placebo-controlled trial. It was conducted at two centers in the United States (Francis I. Proctor Foundation, University of California-San Francisco and Dartmouth-Hitchcock Medical Center) and one in India (Aravind Eye Care). The latter site enrolled the vast majority of the 500 patients in the study population.

Eligible patients had a culture positive bacterial ulcer and were randomly assigned to a 3-week tapering regimen with prednisolone sodium phosphate 1.0% solution or placebo beginning as early as 48 hours after starting topical moxifloxacin 0.5% (Vigamox, Alcon Laboratories).

The primary endpoint was best spectacle-corrected visual acuity (BSCVA) at 3 months. Secondary endpoints included BSCVA at 3 weeks, infiltrate/scar size, time to re-epithelialization, and adverse event rates, including corneal perforation. For all of those measures, there were no significant differences between the steroid and control group.

TAKE-HOME

- ***The Steroids for Corneal Ulcers Trial allays some fears about using a topical corticosteroid as an adjunct to antibiotic treatment in eyes with a bacterial corneal ulcer.***

There were also no other serious safety concerns associated with steroid treatment, although a later analysis in which patients were categorized by pathogen found that steroid use was associated with a significantly larger scar size and a poorer visual outcome in patients infected with *Nocardia* species. Dr. Jeng noted that while *Nocardia spp*. comprised 11% of the pathogens in SCUT, it is a rare cause of bacterial corneal infections in the United States.

About 400 patients were seen at 12 months, and in the overall group, there was no significant difference in mean BSCVA between those who had used the steroid and the controls.

"However, findings from this extended follow-up of patients in SCUT showed that among patients seen at 12 months, mean BSCVA was better by 1 line among those with a non-*Nocardia* infection who had used steroids compared to the controls," Dr. Jeng said.

Recently, data were reported from a group of 50 patients with follow-up to 4 years that showed BSCVA remained stable from 1 to 4 years, and after controlling for vision at enrollment, BSCVA at 4 years was not significantly different between the two study groups.

Per SCUT protocol, patients were to start on their assigned study medication after being on topical moxifloxacin for at least 2 days and up to 4 days. Results of an analysis of outcomes based on time to steroid initiation showed that visual acuity at 3 months was about 1 line better among patients who started the steroid on days 2 or 3 versus those starting on day 4.

"In a suspected bacterial corneal ulcer, I would not start the steroid until I had laboratory results to confirm the diagnosis," Dr. Jeng said. "However, once bacterial etiology is confirmed, SCUT gives reason to start the steroid as soon as possible."

EXAMINING THE LIMITATIONS

The fact that the vast majority of patients in SCUT were enrolled at the India site raises the question of whether the results can be generalized to the U.S. population. In addition, SCUT does not answer questions about which is the best antibiotic to use for treating bacterial corneal ulcers and what is the most appropriate steroid regimen.

"Some critics suggest that the steroid dosing frequency was too low and perhaps there may have been greater benefit with more frequent dosing," Dr. Jeng said. "However, despite the limitations, SCUT is a landmark study that will guide us clinically." ■

BENNIE H. JENG, MD, MS

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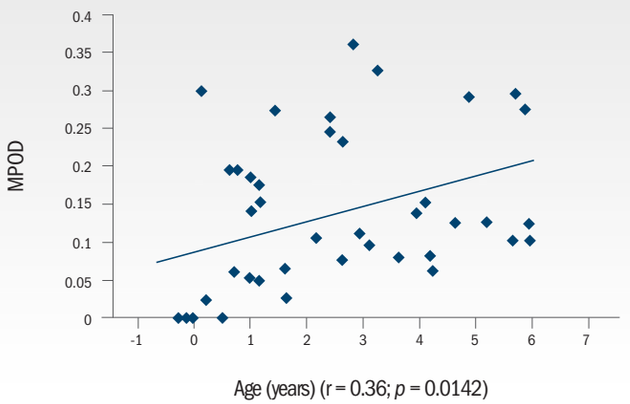
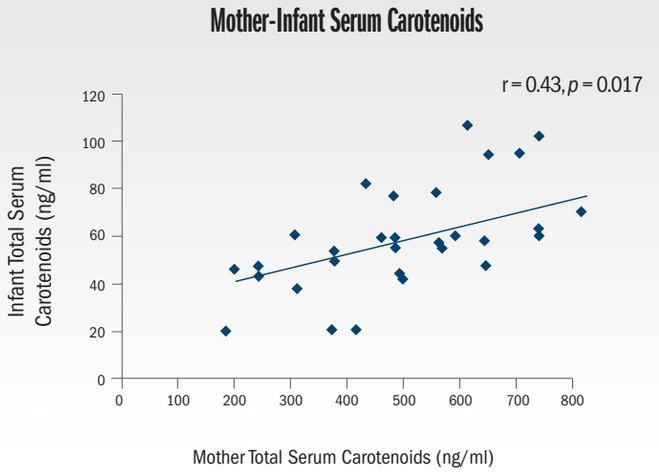
This article was adapted from Dr. Jeng's presentation during Cornea Day at the 2014 meeting of the American Society of Cataract and Refractive Surgery. Dr. Jeng has no relevant financial interests to disclose.

Macular Pigment Optical Density with Age



Changes in peak macular pigment optical density with age.
(Figures courtesy of Paul S. Bernstein, MD, PhD)

Mother/Infant Serum Carotenoids Correlate Significantly



Macular pigment levels may be influenced by maternal nutritional status (high level in serum) that could be passed on to an infant at birth.

VISUAL FUNCTION

(Continued from page 14)

"In that study, we were able to show that macular pigment levels were influenced by maternal nutritional status," Dr. Bernstein said. "If the mother has a high level in her serum and presumably her diet, that's passed on to the baby at birth."

Researchers are now preparing to begin a supplementation study with prenatal vitamins fortified with lutein and zeaxanthin.

"We'll measure the macular pigment in a randomized controlled trial and see how it affects visual function for at least a year," he said.

The study of macular carotenoids may also prove valuable because diseases like AMD are thought to depend on light and oxidative stress that accumulates over one's lifetime, including childhood, Dr. Bernstein said.

CIRCLING BACK TO AMD

Although Dr. Bernstein is focusing now on the role of lutein and zeaxanthin in a younger population, he believes these two carotenoids still play a key role in preventing AMD.

Adult children who bring in their parents with AMD for anti-vascular endothelial growth factor injections often inquire about the connection between nutrition and AMD, Dr. Bernstein explained.

"The answer is, we don't know for certain what they should do," he said. "It was hard enough to do the AREDS and AREDS2 studies to tease out the effects of nutrition on a high-risk elderly population. A comparable prospective study on young healthy people would be prohibitively long and expensive.

"For the adult children, I tell them that diet is very important," Dr. Bernstein said. "Changing your diet at age 40 is very doable, and adding more fruits and vegetables will have benefits that go beyond the eyes. Younger patients can also take supplements, but diet is the preferred way to go."

For someone who has AMD and is older, supplementation may be an easier route. Changing dietary habits in the elderly may be difficult.

"The number one public health approach to preventing AMD will be to improve the American diet, but we still have much to learn about the proper role for lutein and zeaxanthin supplementation for optimal ocular health and performance throughout the entire lifespan," he said. ■

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Join the discussion about the role of the macular pigment carotenoids lutein and zeaxanthin in protecting against AMD at **Facebook.com/OphthalmologyTimes**.

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This article was adapted from Dr. Bernstein's presentation at the 2014 meeting of the Association for Research in Vision and Ophthalmology.

Hypertension, glaucoma link: Exploring pressure interplay

Possible effects, correlations considered in concomitant treatment of chronic disease states

By Liz Meszaros; *Reviewed by Ruth D. Williams, MD*

NAPERVILLE, IL ::

Could the treatment of hypertension be at cross-purposes with the treatment of glaucoma? Ruth D. Williams, MD, explored the possible effects and correlations in concomitant treatment of these two chronic disease states.

In outlining similarities between the treatments of hypertension and glaucoma, she noted:

- **Both are chronic diseases that can be difficult to control.**
- **Treatment of both can require multiple medications and fixed-combination drugs.**
- **Treatment endpoints are poorly defined, and often difficult to achieve, even when defined.**
- **Medication adherence challenges are common in both disease states.**

Clinical trials have attempted to elucidate more on the association between blood pressure—both high and low—and glaucoma, explained Dr. Williams, a glaucoma consultant and partner at the Wheaton Eye Clinic, Naperville, IL.

> 'Ask your patients about blood pressure. If the blood pressure is low, call the cardiologist or internist.' — *Ruth D. Williams, MD*

"Though much work has been done about the elevation of IOP at night—and the systemic hypotension that frequently occurs at night—we have not discussed this very much in our clinical practices in the past 10 years," she said.

OPP RISK FACTOR

Ocular perfusion pressure (OPP) is an important concept and several formulas exist to calculate it. Fundamentally, OPP is the difference between the arterial blood pressure and eye pressure, and a low OPP is a significant risk factor for glaucoma progression.

Dr. Williams reviewed the results from a recent study[1] in which researchers acknowledged the growing evidence that OPP is a glaucoma risk factor. This may be an especially significant factor when IOPs are relatively low, she noted.

Carlos G. de Moraes, MD, presented his study of 85 patients, all with normal-tension glaucoma, and 32% who had both systemic hypertension and normal-tension glaucoma. Dr. Moraes and colleagues monitored ambulatory blood pressures every 30 minutes for 48 hours, at 6-month intervals. One-third of patients had systemic hypertension, and two-thirds were being treated with medications.

Over a mean follow-up of 5 years, 24% of patients had progression by visual field. Low blood pressure during sleep was a strong predictor of visual field progression.

Further, the longer and greater the dips in mean arterial pressure below the daytime average, the greater this risk for progression became compared with patients with normal systemic blood pressure ($p = 0.020$).

Finally, patients with treated hypertension who had nighttime dips had faster progression, she noted.

The authors suggested that glaucoma specialists work with cardiologists and internists to avoid nocturnal hypertension in patients with glaucoma who were taking anti-hypertensive medications, Dr. Williams noted.

"My take-away message from this is: Ask your patients about blood pressure," she said. "If the blood pressure is low, call the cardiologist or internist.

"It's worth a phone call, because when I call cardiologists or internists, most of the time, they have never thought about low blood pressure and how it might affect the optic nerve," Dr. Williams said. "If the blood pressure is low, could it affect the end organ perfusion of other systems, such as brain function?" ■

IS THERE A LINK?

VIDEO Ruth D. Williams, MD, encourages ophthalmologists to consider the role of blood pressure when evaluating patients with glaucoma. Go to **http://bit.ly/106tqAo**

Reference

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Editor's Note: *This article was adapted from Dr. Williams' presentation at the Glaucoma 360° meeting held in association with the Glaucoma Research Foundation and Ophthalmology Times.*

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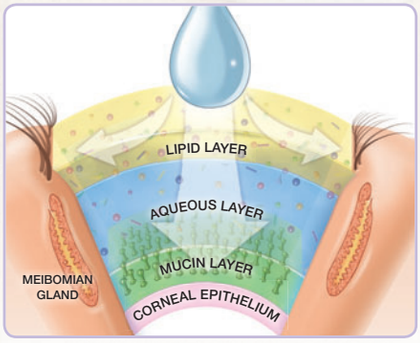

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References: 1. Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care.* 2013;19 (5 suppl):S67-S75. **2.** Korb DR, Blackie CA, Meadows DL, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy.

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Patterns of visual field loss identified by unsupervised machine-learning

VIM successfully determines binocular patterns of glaucomatous defects in SAP visual fields

By Cheryl Guttman Krader; *Reviewed by Christopher Bowd, PhD*

SAN DIEGO ::

IN PREVIOUS research, Christopher Bowd, PhD, and colleagues at the University of California, San Diego, Hamilton Glaucoma Center, demonstrated that an unsupervised machine-learning based classifier—the variational Bayesian independent component analysis mixture model (VIM)—could be applied to monocular standard automated perimetry (SAP) visual fields and monocular frequency-doubling technology (FDT) perimetry visual fields to identify patterns of glaucomatous damage without foreknowledge of diagnosis and without human intervention.

Changes in these patterns over time proved to be a promising method for describing glaucomatous progression, and according to recent evidence, VIM, trained on monocular SAP visual fields, was better at detecting glaucomatous progression than current methods.

Taking their investigations forward, they determined that VIM successfully identified binocular patterns of glaucomatous defects in SAP visual fields and successfully separated patients with glaucoma from unaffected controls.

EVIDENCE

"Our studies show that this method is able to discriminate between glaucomatous and healthy individuals and can automatically find statistically different *binocular* visual field patterns in glaucoma patients," said Dr. Bowd, senior research scientist, director of the Hamilton Glaucoma Center-based Visual Field Assessment Center and co-director of the Hamilton Glaucoma Center-based Imaging Data Evaluation and Analysis Center, Department of Ophthalmology, University of California, San Diego.

"Patterns identified by unsupervised classifiers are more objectively determined than those observed and described by experts, so they are less biased by previous experience and rules of thumb," he said.

He explained that the visual image formed in the brain is based on visual information received from both the eyes. Therefore, it was important to evaluate the performance of the technique for analyzing binocular visual fields because they are more strongly associated with daily activities, such as driving, and also are a better indicator of overall quality of life than the previously studied monocular visual fields.

"Binocular visual fields better reflect the effect of losing part of the entire useful visual field than monocular visual fields and, as the visual field deteriorates, change in binocular visual fields will better reflect the corresponding increase in disability," Dr. Bowd said.

The study included monocular visual fields from both eyes of 543 glaucoma patients and 560 healthy controls.

To be included in the glaucoma cohort, patients had to have repeatable abnormal SAP results by Pattern Standard Deviation or the Glaucoma Hemifield Test in at least one eye.

MORE ON THE STUDY

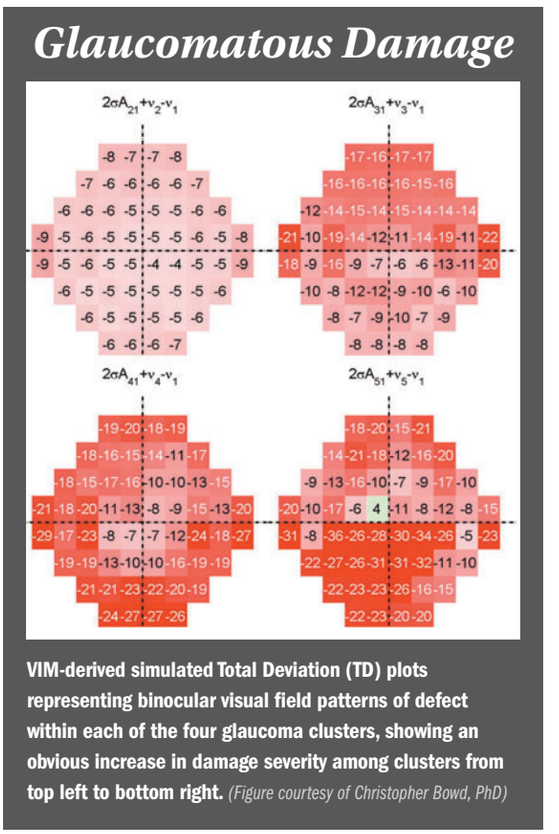
Study participants in the glaucoma cohort had a visual field mean deviation (MD) = -6.15 ± 6.70 dB in their worst eye. Participants were included as healthy controls if they had SAP results within normal limits in both eyes. Healthy controls had a visual field MD in the worst eye of -0.54 ± 1.17 dB.

The study participants were selected from individuals enrolled in the UCSD-based Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES).

Binocular visual fields were constructed through averaging of data from fellow eyes at each visual field location. Input for the VIM analysis included the 56 threshold test points from the constructed binocular visual field and age. Using the data, a total of 720 unsupervised VIM models were generated.

The best model had a specificity of 94% and a sensitivity of 80%. That model separated the binocular visual fields into five clusters or classes, one containing primarily the healthy participants and the other four representing glaucoma patients with increasing levels of severity in the defect pattern that may correlate with the patient's ability to perform everyday tasks.

"Future research will investigate the correlation of cross-sectional and progressing binocular visual field defects with quality of life measures and simulated driving tasks," Dr. Bowd said. ■



VIM-derived simulated Total Deviation (TD) plots representing binocular visual field patterns of defect within each of the four glaucoma clusters, showing an obvious increase in damage severity among clusters from top left to bottom right. *(Figure courtesy of Christopher Bowd, PhD)*

CHRISTOPHER BOWD, PHD

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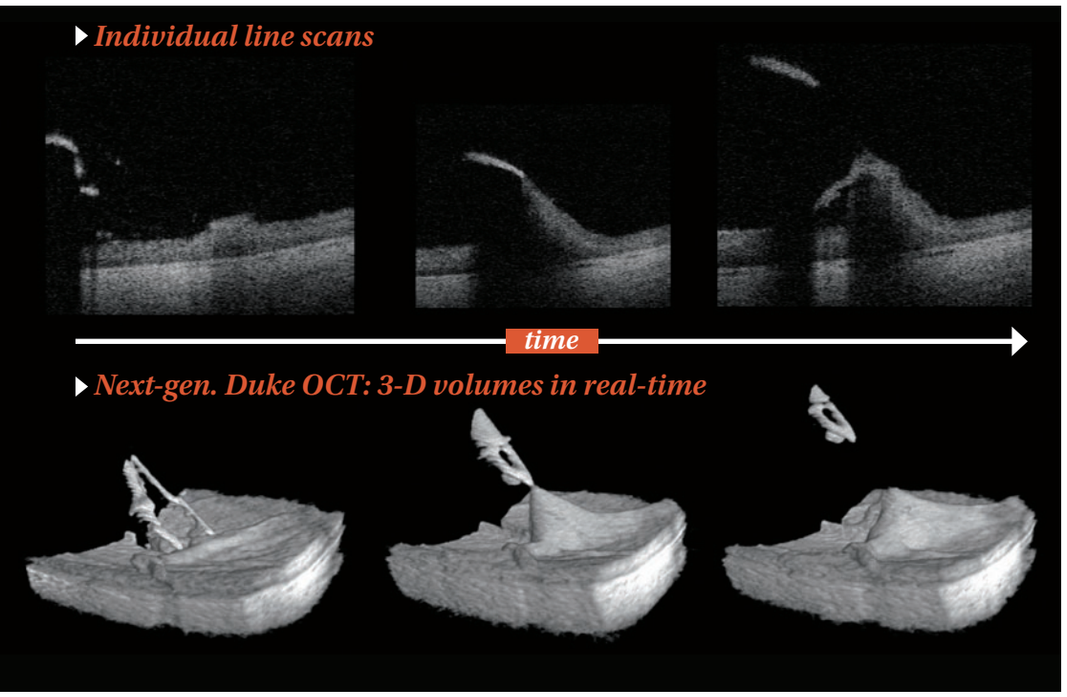
This article was adapted from Dr. Bowd's presentation at the 2014 meeting of the Association for Research in Vision and Ophthalmology. Dr. Bowd did not indicate any proprietary interest in the subject matter..



(FIGURE 1) **Individual line scans capturing a surgical maneuver (top row) may provide information about retina-instrument interactions but are very difficult to interpret out of context. Real-time 3-D volume scans, acquired with a prototype Duke swept-source, based microscope-integrated OCT system, enable improved visualization and contextual perception.** *(Figure courtesy of Paul Hahn, MD, PhD)*

MICROSCOPE-INTEGRATED OCT PROVIDES 3-D IMAGES IN REAL TIME

Next-generation intrasurgical imaging uses swept-source device

By Lynda Charters; *Reviewed by Paul Hahn, MD, PhD*

take-home

- **Advances in imaging technology using swept-source, microscope-integrated optical coherence tomography (OCT) provides detailed and three-dimensional volume images in real time, which cannot be obtained with conventional spectral-domain intraoperative OCT systems.**

DURHAM, NC ::

Intrasurgical imaging using a swept-source, microscope-integrated optical coherence tomography (MIOCT) device is the latest advance in OCT technology that has positively impacted intraoperative human retinal imaging during vitreoretinal surgery.

Intraoperative OCT imaging has been pioneered at Duke University, Durham, NC, by a team led by Cynthia Toth, MD, professor of ophthalmology and bioengineering, and Joseph Izatt, PhD, professor of bioengineering.

"The increased speed and tracking of our next-generation swept-source MIOCT device addresses many of the deficiencies of current intraoperative spectral-domain (SD) platforms and enables seamless real-time, three-dimensional (3-D) imaging of instrument-retina interactions for the first time," said Paul Hahn, MD, PhD, speaking about the swept-source MIOCT prototype unit developed at Duke University.

A number of different types of OCT imaging systems are available for use intraoperatively, but they come with their downsides. A particular handheld SD-OCT instrument (Envisu, Bioptigen) that is approved by the FDA can indeed be used intraoperatively, he noted.


Dr. Hahn

"Much of our current data on intraoperative OCT comes from handheld devices, but they require stopping surgery and therefore cannot obtain real-time OCT images around a moving instrument," said Dr. Hahn, assistant professor of ophthalmology, Duke Eye Center, Duke University School of Medicine.

In addition to the Duke MIOCT unit, other microscope-integrated OCT devices include the Haag-Streit iOCT and the Zeiss Rescan 700. None of these devices is currently commercially available in the United States.

CURRENT, FUTURE OUTLOOK

The major advantage of microscope-integration is the shared optical path with the surgical microscope that enables OCT image acquisition simultaneously with surgical maneuvers.

"These individual scans can be very difficult to interpret out of context," Dr. Hahn said.

Recently, the Duke team finished incorporating next-generation technology into their MIOCT, including use of a swept-source OCT engine to replace the previous spectral-domain engine.

Commenting on the current and future directions, Dr. Hahn said, "MIOCT facilitates an understanding of real-time intrasurgical changes in vitreoretinochoroidal anatomy and their impact on visual outcomes.

"Our next-generation system can push the envelope further, allowing us to develop new surgical techniques and advanced multimodal methods of surgical viewing," Dr. Hahn said. "The possibilities are endless." ■

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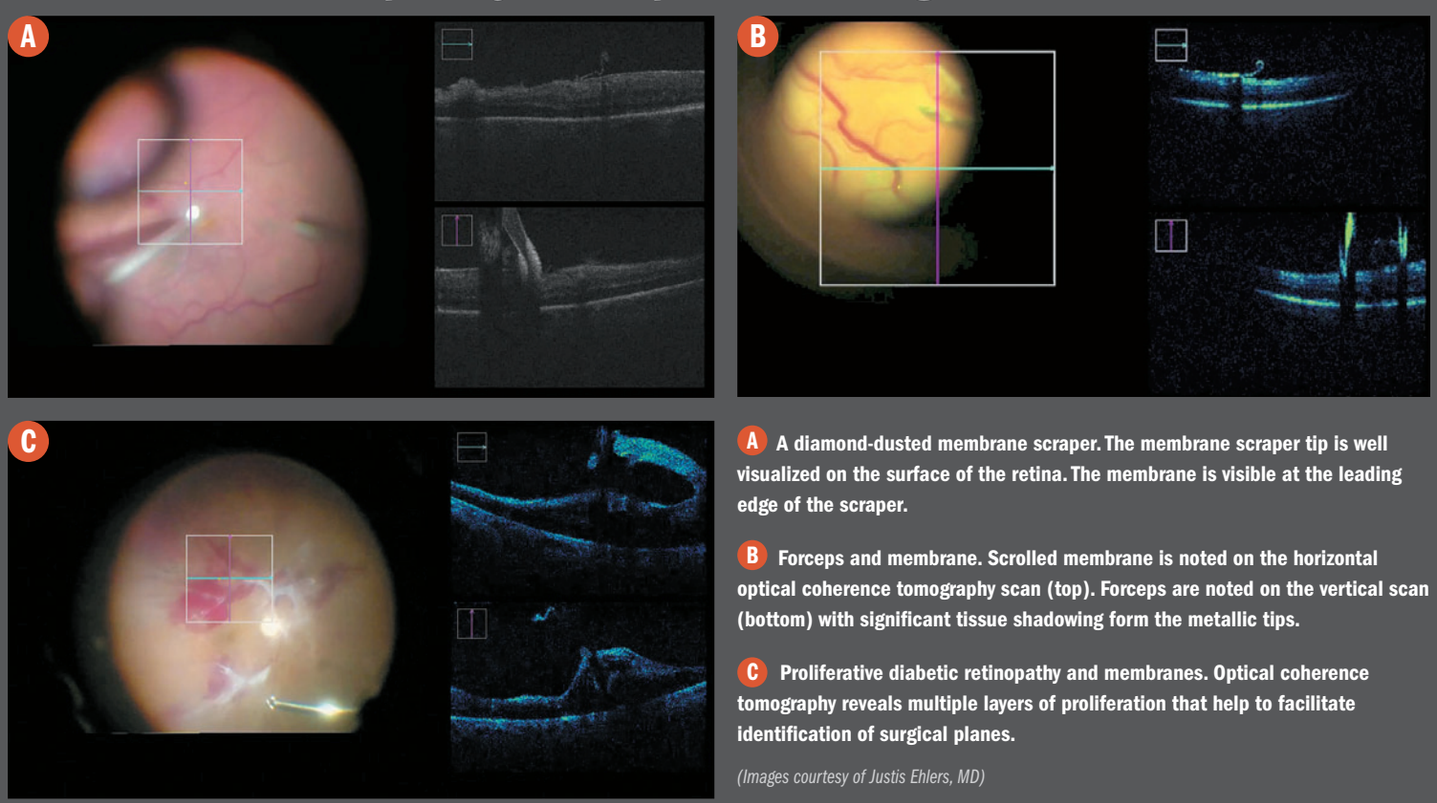
This article was adapted from Dr. Hahn's presentation during the 2014 meeting of the American Society of Retina Specialists. Dr. Hahn has no financial interest in the subject matter.

Using microscope-integrated intraoperative OCT in retina surgery

Information obtained in real-time may change how vitreoretinal surgery is performed

By Michelle Dalton, ELS; *Reviewed by Justis Ehlers, MD*

Examples of Intraoperative Images Obtained



A A diamond-dusted membrane scraper. The membrane scraper tip is well visualized on the surface of the retina. The membrane is visible at the leading edge of the scraper.

B Forceps and membrane. Scrolled membrane is noted on the horizontal optical coherence tomography scan (top). Forceps are noted on the vertical scan (bottom) with significant tissue shadowing form the metallic tips.

C Proliferative diabetic retinopathy and membranes. Optical coherence tomography reveals multiple layers of proliferation that help to facilitate identification of surgical planes.

(Images courtesy of Justis Ehlers, MD)

CLEVELAND ::

INTRAOPERATIVE optical coherence tomography (OCT) that works in real-time can be an invaluable resource for surgeons, said Justis Ehlers, MD.

However, the optimal platform for OCT integration into ophthalmic surgery remains unknown, said Dr. Ehlers, a staff physician on the vitreoretinal service of the Cole Eye Institute, Department of Ophthalmology, Cleveland Clinic.

DISCOVER STUDY

Dr. Ehlers and colleagues are conducting a prospective, multisurgeon, single-center study—the DISCOVER Study—examining the use of multiple microscope-integrated prototypes with real-time surgeon feedback through a heads-up display system, including the Rescan 700 (which is built into the Lumera 700 platform, Carl Zeiss Meditec) and a Cole Eye Institute iOCT System. The DISCOVER Study evaluated both anterior and posterior segment surgery.

"The Rescan 700 is a prototype microscope-integrated iOCT system that is based on the Lumera 700 platform that includes heads-up display of the OCT data stream for the surgeon," said Dr. Ehlers, who discussed the vitreoretinal surgery component.

The interim 4-month analysis included 114 eyes (78 of which presented with vitreoretinal surgery needs). Average age was 61 years, and 47% of the patients were male.

Intraoperative OCT image acquisition was achieved in 77/78 eyes that underwent vitreoretinal surgery (99%). Surgical indications included epiretinal membranes, macular holes, vitreomacular traction, retinal detachment, and IOL subluxation. Of those eyes, 45 (58%) were phakic, 29 (37%) were pseudophakic, and four (5%) were aphakic.

Retinal detachment and epiretinal membrane were the most frequent diagnoses (23% and 31%, respectively). Vitreoretinal imaging was accomplished with both non-contact wide-angle and a contact lens viewing system.

HEADS-UP DISPLAY SYSTEM

"Initially, surgeons may have challenges adapting to the heads-up display system while performing particularly delicate manueuvers," Dr. Ehlers said, but he believes this is primarily attributed to the typical learning curve rather than a true deterrent to the system.

Additionally, at any time the heads-up display and OCT imaging system can be turned

OUR SCIENCE. YOUR ART. THEIR VISION.

NOW APPROVED FOR DIABETIC MACULAR EDEMA (DME)

As Demonstrated in 2 Pivotal, Phase 3 Trials in Patients With DME Evaluating Mean Change in BCVA* at 52 Weeks vs Baseline[1]

EYLEA® (aflibercept) Injection Offers Extended Dosing in DME—2-mg Every 8 Weeks Following 5 Initial Monthly Doses[1]

Initial Dosing	Follow-Up Dosing
5 Initial 2-mg Injections Monthly (Every 4 Weeks)	2-mg Every 2 Months (Every 8 Weeks)

Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

*BCVA = best-corrected visual acuity, as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

IMPORTANT PRESCRIBING INFORMATION FOR EYLEA® (aflibercept) INJECTION

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.
- Macular Edema following Central Retinal Vein Occlusion (CRVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.
- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs in the VIEW 1 and VIEW 2 wet AMD studies in patients treated with EYLEA was 1.8% during the first year. The incidence of ATEs in the COPERNICUS and GALILEO CRVO studies was 0% in patients treated with EYLEA compared with 1.4% in patients receiving sham control during the first six months. The incidence of ATEs in the VISTA and VIVID DME studies during the first year was 3.3% in the combined group of patients treated with EYLEA compared with 2.8% in the control group.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.
- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, retinal detachment, cataract, intraocular pressure increased, and vitreous detachment.

For more information, visit www.EYLEA.com.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. July 2014.

Please see brief summary of full Prescribing Information on the following page.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

07/2014
LEA-0311

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

INDICATIONS AND USAGE

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Central Retinal Vein Occlusion (CRVO), and Diabetic Macular Edema (DME).

DOSAGE AND ADMINISTRATION

FOR OPHTHALMIC INTRAVITREAL INJECTION. EYLEA must only be administered by a qualified physician.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months),followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

Macular Edema Following Central Retinal Vein Occlusion (CRVO). The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly).

Diabetic Macular Edema (DME). The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. The glass vial is for single use only. Remove the protective plastic cap from the vial. Clean the top of the vial with an alcohol wipe. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom edge of the vial. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle. Remove the filter needle from the syringe and properly dispose of the filter needle. **Note:** Filter needle is **not** to be used for intravitreal injection. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip.

When ready to administer EYLEA, remove the plastic needle shield from the needle. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe.

Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution for intravitreal injection.

CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (*see Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (*see Dosage and Administration and Patient Counseling Information*).

Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (*see Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (*see Dosage and Administration*).

Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence in the VIEW1 and VIEW2 wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the COPERNICUS and GALILEO CRVO studies during the first 6 months was 0% (0/218) in patients treated with EYLEA 2 mg every 4 weeks compared with 1.4% (2/142) in patients receiving sham treatment. The incidence in the VIVID and VISTA DME studies during the 52 weeks was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Injection Procedure. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, retinal detachment, cataract, intraocular pressure increased, and vitreous detachment.

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

A total of 2620 patients treated with EYLEA constituted the safety population in six phase 3 studies. Among those, 2019 patients were treated with the recommended dose of 2 mg.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Central Retinal Vein Occlusion (CRVO). The data described below reflect exposure to EYLEA in 218 patients with macular edema following CRVO treated with 2-mg dose in 2 double-masked, controlled clinical studies (COPERNICUS and GALILEO) for 6 months.

Table 2: Most Common Adverse Reactions (≥1%) in CRVO Studies

Adverse Reactions	EYLEA (N=218)	Control (N=142)
Eye pain	13%	5%
Conjunctival hemorrhage	12%	11%
Intraocular pressure increased	8%	6%
Corneal erosion	5%	4%
Vitreous floaters	5%	1%
Conjunctival hyperemia	5%	3%
Foreign body sensation in eyes	3%	5%
Vitreous detachment	3%	4%
Lacrimation increased	3%	4%
Injection site pain	3%	1%
Vision blurred	1%	<1%
Intraocular inflammation	1%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were cataract, eyelid edema, corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME)

The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) for 52 weeks.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%
Eye pain	9%	6%
Cataract	8%	9%
Vitreous floaters	6%	3%
Corneal erosion	5%	3%
Intraocular pressure increased	5%	3%
Conjunctival hyperemia	5%	6%
Vitreous detachment	3%	3%
Foreign body sensation in eyes	3%	3%
Lacrimation increased	3%	2%
Vision blurred	2%	2%
Intraocular inflammation	2%	<1%
Injection site pain	2%	<1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, eyelid edema, corneal edema, retinal detachment, injection site hemorrhage, and retinal tear.

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

In the wet AMD, CRVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 52 weeks (wet AMD), 24 weeks (CRVO), or 52 weeks (DME) antibodies to EYLEA were detected in a similar percentage range of patients. In the wet AMD, CRVO, and DME studies, there were no differences in efficacy or safety between patients with or without immunoreactivity.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

Geriatric Use. In the clinical studies, approximately 76% (1996/2610) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 47% (1229/2610) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

PHARMACOKINETICS

Specific Populations. Patients with Renal Impairment. Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a CRVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, CRVO, or DME patients.

PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (*see Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (*see Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

U.S. License Number 1760

Issue Date: July 2014
Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

LEA-0294

off during surgery with foot-pedal surgeon control, he said.

"Generally, there was rapid adaption," he said. "Surgeons using this system included a wide range of surgical experience from 20 years-plus to first-year retina fellows."

The heads-up display system provided real-time feedback to the surgeon regarding anatomic configurations during surgery and allowed for visualization of instrument-tissue interactions. The overwhelming number of surgeons preferred the heads-up display and real-time data acquisition.

However, in 5% of cases, the device was judged to interfere with the case, Dr. Ehlers said.

Several adverse events occurred during the surgical procedures, such as elevated IOP and epithelial defects. However, no adverse events were directly attributed to the iOCT system.

"In addition to cost, the only real disadvantage to the system is the potential for increased time of surgery," Dr. Ehlers said. "On the other hand, there are certain cases where the system speeds up the surgery because it confirms the surgeon has done everything he or she needed to do before the surgeon necessarily knew it. You're potentially able to end surgery more quickly."

CHANGING SURGICAL STRATEGIES

Residual membranes, occult formation of full-thickness macular holes, and confirmation of optimal IOL position were identified with the iOCT system resulting in alterations to the surgical decision-making process. (See Images A, B, and C on Page 24 for examples of the images obtained intraoperatively.)

The iOCT showed residual membrane requiring additional peeling in 14% of cases (5/36) where the surgeon believed peeling was complete. There was complete membrane peel in 11% of cases (4/36) where the surgeon thought additional peeling was necessary.

The real questions that we want to answer, suggested Dr. Ehlers, are: How does iOCT impact long-term patient outcome, and what outcomes would these patients have had without the iOCT?

Until there are "masked, randomized trials, we're not going to know the definitive answer," he said, adding the Cole Eye Institute group is in the planning stages for those studies.

COINCIDENCE?

"Re-proliferation or recurrence of epiretinal membrane is typically thought to occur in the 5% to 15% range," he said. "What if, in fact, surgeons aren't getting OCTs until the post-operative 3-month time frame, and they come to the conclusion that there was re-proliferation? But what if they just didn't get it all during the original surgery? Our preliminary data seems to support that in around 10% of cases, surgeons are not realizing that residual membranes are present without iOCT."

While acknowledging it's still too soon to make a definitive statement, the DISCOVER study comprised surgeons with all levels of experience yet still found 14% of peels were incomplete based on iOCT data.

"This is a number that keeps popping up," he said. "Our PIONEER study that was recently published (2-year results with more than 500 patients) used an external microscope-mounted intraoperative OCT and we found similar numbers there, too—in about 15% of epiretinal membrane cases, the OCT revealed membranes the surgeon thought had been removed."

Through the use of iOCT, "we are learning that we don't understand what all is going on in the eye when we're manipulating it with surgery," Dr. Ehlers said. "We have a lot of things to learn about what our surgical manipulations do to the architecture of the eye and how those subtle architectural alternations may have implications for outcomes.

"The technology may be in a similar stage to when OCT was first introduced in the clinic," he said. "Many people didn't believe that it would pay a significant role in the clinical care of vitreoretinal patients, and now we're using it on 70% of our patients who come through our clinics. We still have a lot to learn about the benefits of this technology." ■

take-home

- **Real-time intraoperative OCT utilizing a microscope-integrated prototype with a heads-up display surgeon feedback system is explored in the DISCOVER Study.**

JUSTIS EHLERS, MD

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This article was adapted from Dr. Ehlers' presentation at the 2014 meeting of the American Society of Retina Specialists. Dr. Ehlers did not indicate any proprietary interest in the subject matter.

Novel strategies for RVO on horizon

By Cheryl Guttman Krader

BOSTON ::

THE ADVENT OF anti-vascular endothelial growth factor (VEGF) therapy has been a tremendous advance for retinal vein occlusion (RVO), but many other opportunities exist, said Joan W. Miller, MD, Henry Willard Williams Professor of Ophthalmology, chief and chair of ophthalmology, Harvard Medical School.

Understanding of the events involved in alteration of the blood-retinal-barrier that leads to macular edema after RVO provides a basis for identifying potential therapeutic interventions. Dr. Miller discussed a role for treatments targeting cellular junction proteins and metabolic alterations.

Pertaining to the latter, she noted that work being led by her colleague Demetrios G. Vavvas, MD, PhD, is focusing on aminoimidazole carboxamide ribonucleotide (AICAR) as a possible treatment for macular edema. AICAR, currently being investigated as a cardioprotectant in phase III clinical trials, is a small molecule AMP analogue that activates AMP kinase. Interest in AICAR as a treatment for macular edema relates to evidence suggesting that AMP kinase has a protective role for vascular permeability. Results from studies investigating AICAR show that it suppresses endocytosis, inhibits MMP-9, and inhibits VEGF-induced vascular tube formation.

AICAR has been shown to promote endothelial and pericyte cell survival as well as to prevent aging changes in retinal neurons, she said.

Neuroprotection strategies are also of interest for treatment of RVO since photoreceptor degeneration is the ultimate cause of vision loss after RVO. Findings from studies in models of retinal disease showing that there are redundant cell death pathways indicate that preservation of photoreceptors may require combination therapy targeting both apoptosis and programmed necrosis, Dr. Miller said.

In addition, stem cell therapy may have a role for delivery of trophic factors or for integration and repopulation of retinal tissue. ■

New vitrectomy technologies advance precision, efficiency during surgery

Faster cut rate and smaller gauge add benefits without compromises, notes physician

By Cheryl Guttman Krader; *Reviewed by Pravin Dugel, MD*

LOS ANGELES ::

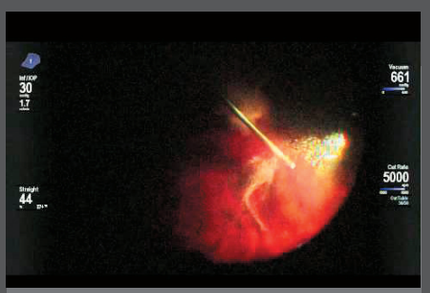
A NEW ultra-high-speed vitrectomy cutting probe operating at 7,500 cuts per minute (Ultravit High Speed Vitrectomy Probe, Alcon Laboratories) combined with use of 27+ gauge instrumentation enables safer and more efficient vitrectomy surgery, according to Pravin Dugel, MD.

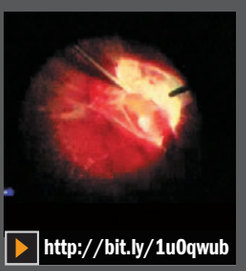
Dr. Dugel

"Cutting at a faster rate creates less traction on the collagen fibrils that in turn reduces the chance of iatrogenic tears and retina incarceration, while use of smaller-gauge instrumentation allows a smaller incision size but more importantly improves precision for greater safety and efficiency," said Dr. Dugel, managing partner, Retinal Consultants of Arizona, Phoenix, and clinical professor, Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles.

"The 27+ gauge instrumentation with the ultra-high-speed cutter is an appealing combination, because it allows me to remove fibrous tissue safely and effectively in a complicated traction detachment without the need for multiple instrument exchanges," Dr. Dugel said.

Capabilities and Sphere of Influence





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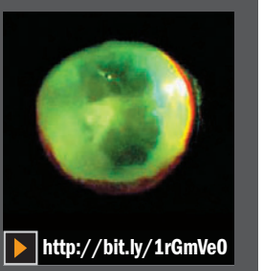

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VIDEO To watch the flow rate comparision go to **http://bit.ly/1pb5Miq**. View more videos (at right) for cases of 27-g complicated TRD with prop reflux and SOI, 27-g endophthalmitis/very dense membranes, and large and small gauge.

(Videos courtesy of Pravin Dugel, MD)

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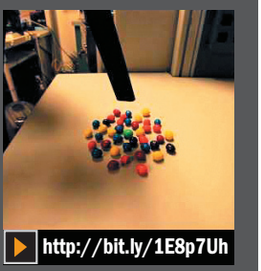

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FLUIDICS OF VITRECTOMY

The benefit of smaller-gauge instrumentation is understood on a concept Dr. Dugel named "the sphere of influence" that relates to area of fluidic collateral damage. As instrument gauge size becomes smaller, so does the sphere of influence, and this decreases the amount of flow needed to attract tissue. Less flow translates into less collateral fluidic damage and therefore greater surgical precision.

Dr. Dugel explained this concept using different size vacuum cleaners to retrieve a certain color candy-coated chocolate from a group of candies. The ability to pick up the single-color candy by itself was improved using a hose with a smaller diameter. (See videos this page)

"If the candy of interest represents fibrous tissue and the other candies represent normal retina, it is clear that using a vitrectomy instrument with a larger gauge that has a larger sphere of influence causes more collateral damage and is associated with increased chance of incarcerating normal retinal tissue," Dr. Dugel said. "Thus, surgical precision is improved with the use of smaller-gauge instrumentation."

Dr. Dugel acknowledged that concerns have been raised regarding the stiffness and procedural speed of 27-gauge instrumentation. He noted that the flexibility of the instrumentation increases with decreasing gauge size (i.e., 27 gauge is slightly more flexible than 25 gauge).

"However, the clinically relevant issue is whether there is sufficient stiffness, and for me, with the use of wide-angle viewing and reinforcement of the shaft, the stiffness of the 27+ gauge instrumentation is absolutely adequate for what I need to do," he said.

In terms of how gauge size affects procedural speed, Dr. Dugel noted that flow rate is lower using smaller-gauge instrumentation.

However, maximizing flow rate is not a goal for improving vitrectomy surgery because it introduces the increased risk of iatrogenic retinal tears and retinal incarceration.

"What we are aiming for is to have an adequate and appropriate amount of flow, and that is achievable using the 27+ gauge instrumentation," Dr. Dugel said.

"Available studies show that by increasing vacuum when operating with the 27+gauge probe, we can increase the flow rate so that it is the same as with 25-gauge instrumentation and very close to that of 23-gauge instrumentation," he said. ■

take-home

A retina specialist explains why vitrectomy surgery is safer and more efficient using a new ultra-high-speed vitrectomy cutting probe combined with 27+ gauge instrumentation.

PRAVIN DUGEL, MD

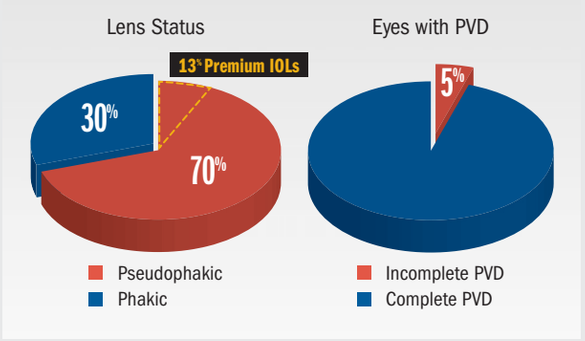
E: *pdugel@gmail.com*

This article was adapted from Dr. Dugel's presentation at the 2014 meeting of the American Society of Retina Specialists. Dr. Dugel is a consultant to Alcon Laboratories and Novartis.

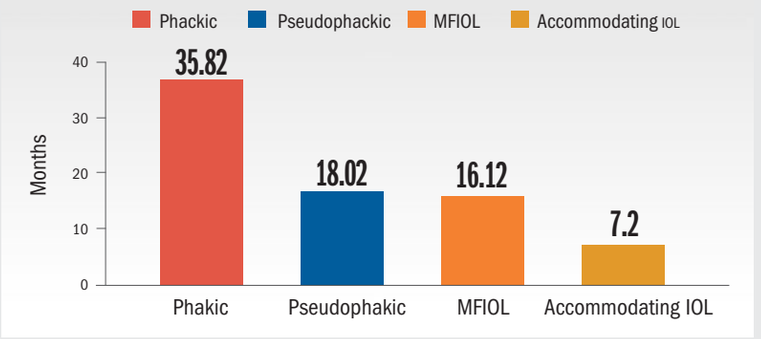
Small-gauge vitrectomy for floaters

Though rare, complications may occur; patients should be made aware prior to surgery

By Michelle Dalton; *Reviewed by James H. Osher, MD*



Lens status and posterior vitreous detachment: baseline.



Time between onset of symptoms and pars plana vitrectomy (PPV).

(Figures courtesy of James H. Osher, MD/Vitrectomy for Floaters Study Group)

CINCINNATI ::

SMALL-GAUGE PARS plana vitrectomy (PPV) for symptomatic floaters is associated with few but potentially serious complications, said James M. Osher, MD, on behalf of the Vitrectomy for Floaters Study Group (VFSG).

"Floaters most commonly result from posterior vitreous detachment (PVD) or vitreous syneresis," explained Dr. Osher, who began this study with Michael Lai, MD, PhD, during his surgical retina fellowship at Retina Group of Washington/Georgetown University. Dr. Osher is now assistant professor of ophthalmology at the Cincinnati Eye Institute/University of Cincinnati.

"Vitrectomy for symptomatic vitreous floaters has become more widespread with the use of small-gauge instrumentation, which affords a higher safety profile," he added.

To that end, the VFSG initiated a study to identify risk factors for symptomatic vitreous floaters and to analyze the intraoperative and postoperative complications of small-gauge PPV. The retrospective interventional case series included 204 eyes of 153 patients who underwent 23- or 25-gauge PPV for vitreous floaters over a 45-month period at a single private retina practice.

take-home

James M. Osher, MD, identifies the patient characteristics and reviews some rare complications with small-gauge vitrectomy for vitreous floaters.

Preoperative data recorded included length of symptoms, visual acuity, IOP, lens status, and IOL type. Premium IOL patients were considered those with multifocal or accommodating lenses (toric lenses were not considered premium for the purposes of this study).

Intraoperatively, the group evaluated vitrectomy gauge, PVD induction, and presence of retinal tears. Finally, postoperative data included visual acuity, IOP, cataract development, and complications.

In short, Dr. Osher said "premium IOL patients may be more symptomatic from vitreous floaters and, therefore, elect surgical intervention sooner than patients with monofocal, toric, or crystalline lenses."

WHAT THE STUDY FOUND

The mean age of the patients was 62.8 years (40 to 88) and mean follow-up was 8.7 months (1 to 41). Sixty-four percent (n = 131) of eyes were pseudophakic, with 15% (n = 19) of IOLs being either multifocal or accommodating. Most eyes (94.1%) underwent 25-gauge PPV.

Intraoperative PVD was present in 191 eyes (78.3%). PVD induction was performed in the remaining 13 eyes. Intraoperative retinal tears were identified in 7 eyes, 2 of which had PVD induction ($p < 0.05$).

Postoperative complications included one case each of endophthalmitis and retinal detachment; 15 eyes had a transient hypotony of less than 5 mm Hg, and 14 eyes had a transient IOP of more than 25 mm Hg.

Thirty-four percent of phakic eyes underwent cataract surgery during the follow-up period, with the mean time to surgery of 8.5 months. Forty-five percent of phakic eyes showed no progressive lens changes.

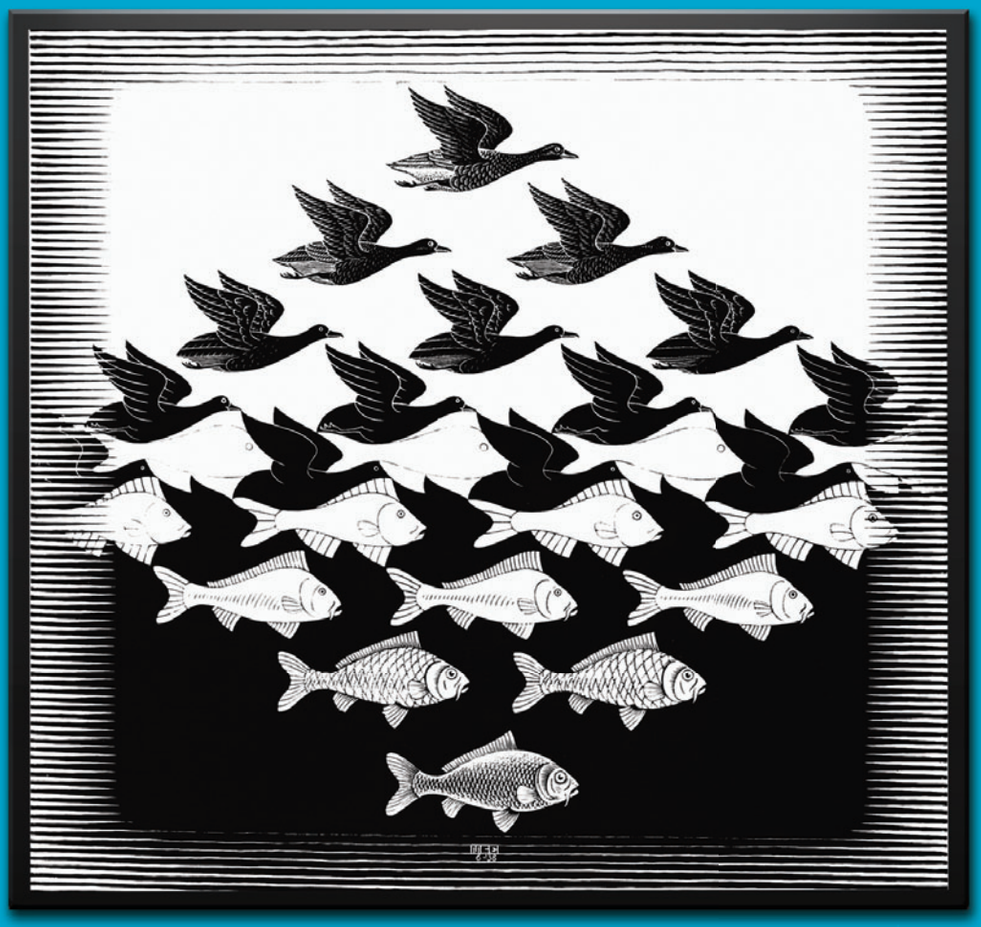
Postoperative visual acuity in pseudophakic eyes remained stable at 20/25 at postoperative months 3 and 6, but decreased slightly from 20/25 to 20/30 ($p = 0.01$) in phakic eyes from month 3 to month 6. The time interval between symptom onset and PPV was shorter for patients with premium IOLs than other patients (mean 13.8 versus 23.6 months).

However, the difference did not reach statistical significance ($p = 0.22$).

"There are three possibilities for the increased symptoms in the premium lens patients," Dr. Osher said.

"First, there may be an actual optical dif-

*(Continues on page 31 : **PPV**)*



Indication and Usage
Diabetic Macular Edema
OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Dosage and Administration
FOR OPHTHALMIC INTRAVITREAL INJECTION.
The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

IMPORTANT SAFETY INFORMATION
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Adverse Reactions
Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous

UPDATED DME INDICATION

SEE DME Differently.

- **The pathophysiology**
  — An **inflammatory cascade** plays a key role[1-5]
- **The therapeutic targets**
  — Suppress multiple **inflammatory cytokines**[6]
- **The clinical results**
  — Achieve clinically significant **3-line gains** in BCVA[6,*]

Now for use in the general DME population

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® (dexamethasone intravitreal implant) patients versus 4% of sham patients. 42% of the patients who received OZURDEX® (dexamethasone intravitreal implant) were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® (dexamethasone intravitreal implant) group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

Please see Brief Summary of full Prescribing Information on next page.

*Best-corrected visual acuity.

Ozurdex® (dexamethasone intravitreal implant) 0.7 mg

1. Jain A, Varshney N, Smith C. The evolving treatment options for diabetic macular edema. *Int J Inflam.* 2013;2013:689276. **2.** Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol.* 2009;54(1):1-32. **3.** Ehrlich R, Harris A, Ciulla TA, Kheradiya N, Winston DM, Wirostko B. Diabetic macular oedema: physical, physiological and molecular factors contribute to this pathological process. *Acta Ophthalmol.* 2010;88(3):279-291. **4.** Scholl S, Kirchhof J, Augustin AJ. Pathophysiology of macular edema. *Ophthalmologica.* 2010;224(suppl 1):8-15. **5.** Zhang W, Liu H, Al-Shabrawey M, Caldwell RW, Caldwell RB. Inflammation and diabetic retinal microvascular complications. *J Cardiovasc Dis Res.* 2011;2(2):96-103. **6.** OZURDEX® Prescribing Information.

ALLERGAN Retina

www.Ozurdex.com APC52TE14 143433

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE

Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Diabetic Macular Edema

OZURDEX® is indicated for the treatment of diabetic macular edema.

CONTRAINDICATIONS

Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product *[see Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection *[see Patient Counseling Information]*.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses *[see Adverse Reactions]*.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

ADVERSE REACTIONS

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

Adverse reactions associated with ophthalmic steroids including OZURDEX® include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Following a second injection of OZURDEX® (dexamethasone intravitreal implant) in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in the table below were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Ocular		
Cataract[1]	166/243[2] (68%)	49/230 (21%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

[2] 243 of the 324 OZURDEX® subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

	Treatment: N (%)	
IOP	**OZURDEX®** N=324	**Sham** N=328
IOP elevation ≥10 mm Hg IOP change from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization,1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

Cataracts and Cataract Surgery

At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

OphthalmologyTimes.com
Online Exclusive

STUDY: HOME-MONITORING DEVICE IDENTIFIES NEW CNV FASTER

THE HOME MONITORING OF THE EYE (HOME) STUDY—part of the Age-Related Eye Disease 2 (AREDS 2) study—indicated that earlier detection of new choroidal neovascularization (CNV) using the preferential hyperacuity perimetry device (ForeseeHome, Notal Vision Ltd.) may identify AMD progression faster than when relying on standard care alone, which includes prescheduled appointments and use of the Amsler grid. The monitoring device can identify metamorphopsia in patients with wet AMD before they notice any visual changes, making early treatment and better visual outcomes possible. Go to http://bit.ly/1pibejp

PPV

(Continued from page 27)

ference in premium IOLs compared [with] monofocal IOLs that makes floaters more symptomatic," Dr. Osher said. "Second, patients who are more likely to opt for a premium IOL have higher expectations and therefore are more bothered by/sensitive to any imperfections in their vision.

"And, finally, the personality of patients who select premium IOLs by nature may also predispose them to become more bothered by floaters," he said.

Because intraoperative retinal tears are more common if a PVD is induced (an almost five-fold increase compared with eyes with a pre-existing PVD), Dr. Osher recommends a complete scleral-depressed exam at the conclusion of surgery to check for tears in the retina.

For the cataract surgeon who may implant the premium lens, Dr. Osher said "our observation of increased symptoms with premium IOLs should prompt the cataract surgeon to discuss this possibility with the patient, especially if large floaters are observed on the preoperative exam."

Referral to a retina specialist or an ophthalmologist comfortable with performing a scleral-depressed retina exam should take place with any new onset of floaters to evaluate for retinal tears. Patient should be referred for possible surgical intervention when the symptoms interfere with aspects of the patient's life and are more than a nuisance. Similar referral patterns should be considered for a phakic patient.

One of the biggest strengths of this study was the number of cases—it is the largest study to date that examined small-gauge PPV for floaters, according to Dr. Osher.

"We believe that small-gauge vitrectomy for floaters is a viable option in the symptomatic patient," he said. "While the complication rate is very low, vision-threatening complications do occur and patients should be made aware of this prior to moving forward with surgery."

Pseudophakic patients or eyes with PVD may be better candidates for small-gauge PPV, he noted. ■

JAMES M. OSHER, MD
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This article was adapted from Dr. Osher's presentation at the 2014 meeting of the American Society of Retina Specialists. He did not indicate any proprietary interest in the subject matter.

Case studies: Laser therapy, injection paradigms for treatment of DME

Approaches can be used together in some cases; better suited as stand-alone procedures in others

By Manish Nagpal, MD, *Special to* Ophthalmology Times

GUJARAT, INDIA ::

WHEN TREATING diabetic macular edema (DME), ophthalmologists often face the choice of which treatments should be used—either alone or in combination—that best prevent further damage to the retina, correct vision loss, and prevent eventual blindness.

Many tools are available for treating DME and edema in general—two of which I have found to be successful: laser therapy, which has been proven to be extremely effective, and anti-vascular endothelial growth factor (VEGF) injections, which should be used moderately due to potential risk factors.

In certain cases, these two treatments can be used together. In others, they are better suited as stand-alone procedures.

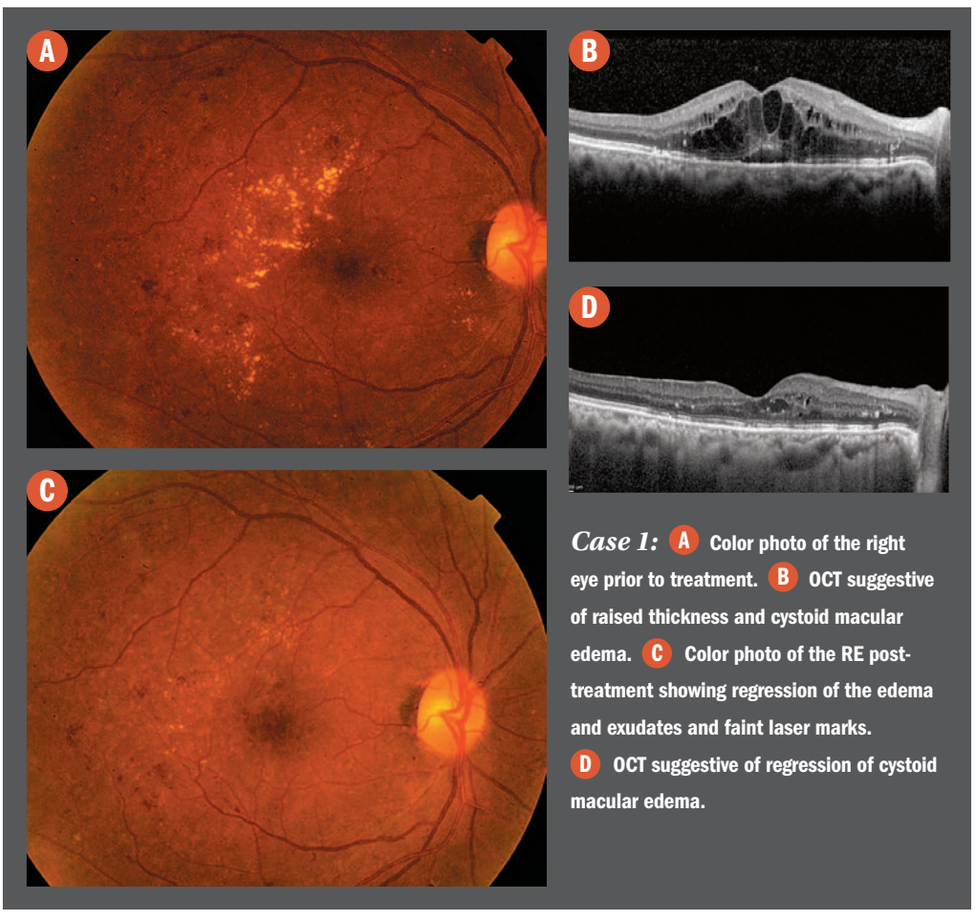
WHEN TO USE LASER

When assessing a patient with DME, I first determine how diffuse is the edema. I examine the eye using ocular coherence tomography (OCT). If the edema is not diffuse, I usually treat the eye with laser therapy alone using pattern scanning laser treatment with algorithm-based software (Endpoint Management, Topcon Medical Laser Systems). The software applies a user-defined percentage of the titration burn to deliver non-destructive laser treatment that can utilize a grid for more accurate burn patterns.

The software has a feature called "Landmarks" that can outline the macular grid with a few visible endpoints and allow me to see where I have applied the laser, even though most of the treatment is not ophthalmoscopically visible. This gives confidence that I have treated the entire area, and do not run the risk of overlapping burns or missing an important area.

WHEN TO USE BOTH

If examination reveals that the edema is not well defined and in small areas, or more diffuse, I combine laser therapy and injections for the best possible results. One of the benefits of combination therapy is that the frequency of anti-VEGF injections can be reduced, which means less risk of side effects or complications to the patient.



Case 1: **A Color photo of the right eye prior to treatment. B OCT suggestive of raised thickness and cystoid macular edema. C Color photo of the RE post-treatment showing regression of the edema and exudates and faint laser marks. D OCT suggestive of regression of cystoid macular edema.**

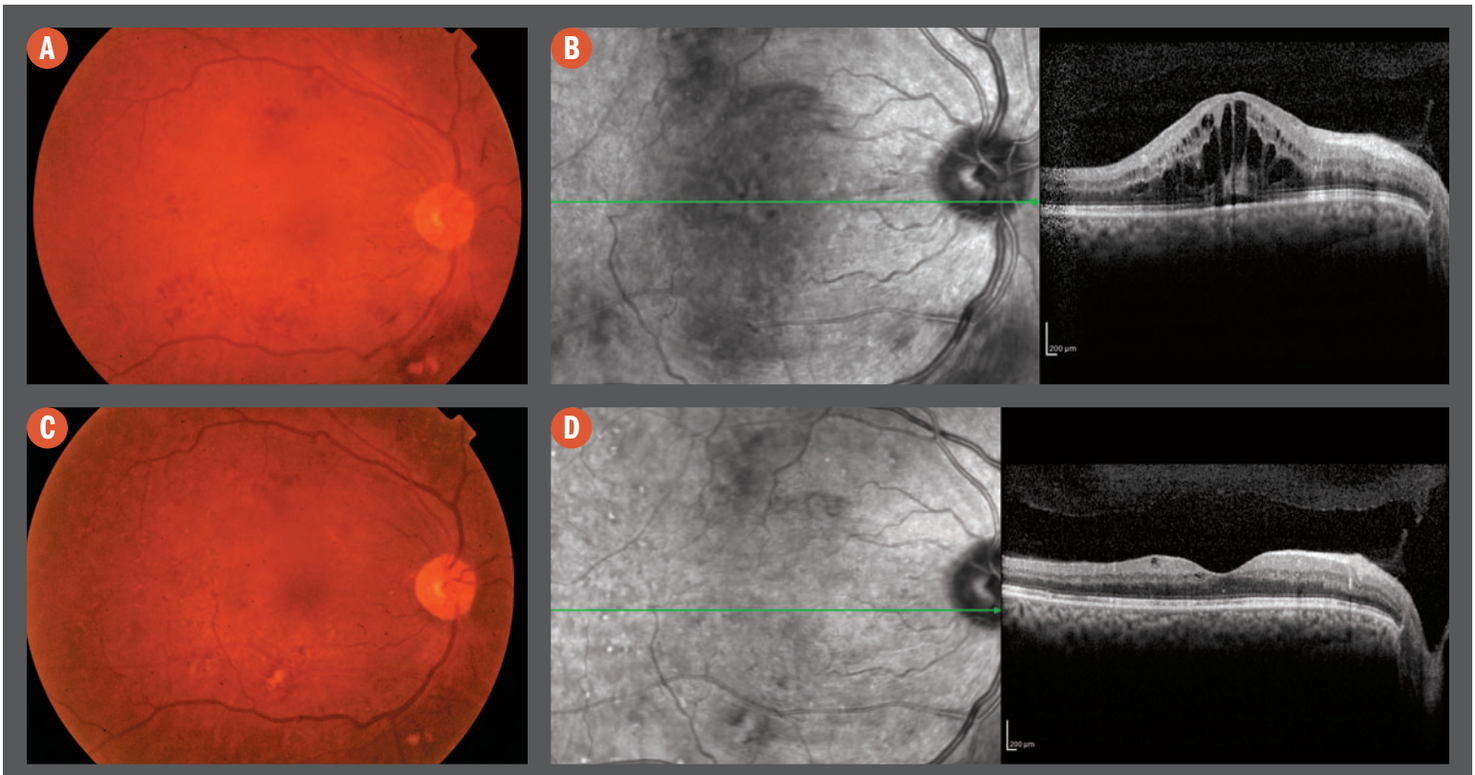
I also use combination therapy in cases of macular edema due to branch vein occlusion. For a patient with acute branch vein occlusion, I recommend three anti-VEGF treatments over the course of a month. At the second injection appointment, I perform a mild grid laser to the area using a 30% to 40% setting. In this case, I don't want to achieve a dense white burn. I just want to "tickle" the retinal pigment epithelium (RPE) cells so that they help regress the edema faster.

PATIENT CASES

Several cases illustrate this technique and treatment paradigm.

Case 1: A 50-year-old diabetic male presented with a reduction in vision to about 20/80, which had occurred over the course of 1 month. During examination, I discovered circinates in the eye and some hemorrhages temporal to the fovea. I ordered an OCT, which revealed significant cystoid macular edema. I advised a combination of anti-VEGF injections and grid laser, which was performed using 100 µm spot burns at 200 mW power titration and a setting of 40%. I applied a semi-circular grid pattern and followed this with an injection of ranibizumab (Lucentis, Genentech). At the 1-month visit, the patient had good regression of the edema and his visual acuity had improved to 20/20. At the 4-month postoperative visit, he remained stable.

Case 2: A 52-year-old diabetic female had a noticeable decrease in vision in her right eye. At the time of her initial evaluation, her vision was 20/200, and a fundus evaluation revealed diffuse macular edema and hemorrhages around the macular area. I also advised



Case 2: **A Color photo of the right eye prior to treatment revealing diffuse edema and hemorrhages. B OCT corresponding to the color photo revealing extensive macular edema and cystoid spaces at the fovea. C Color photo of the right eye post-treatment revealing regression of the edema and hemorrhages. D OCT of the right eye post-treatment revealing regression of the macular edema as well as cystoid spaces.**

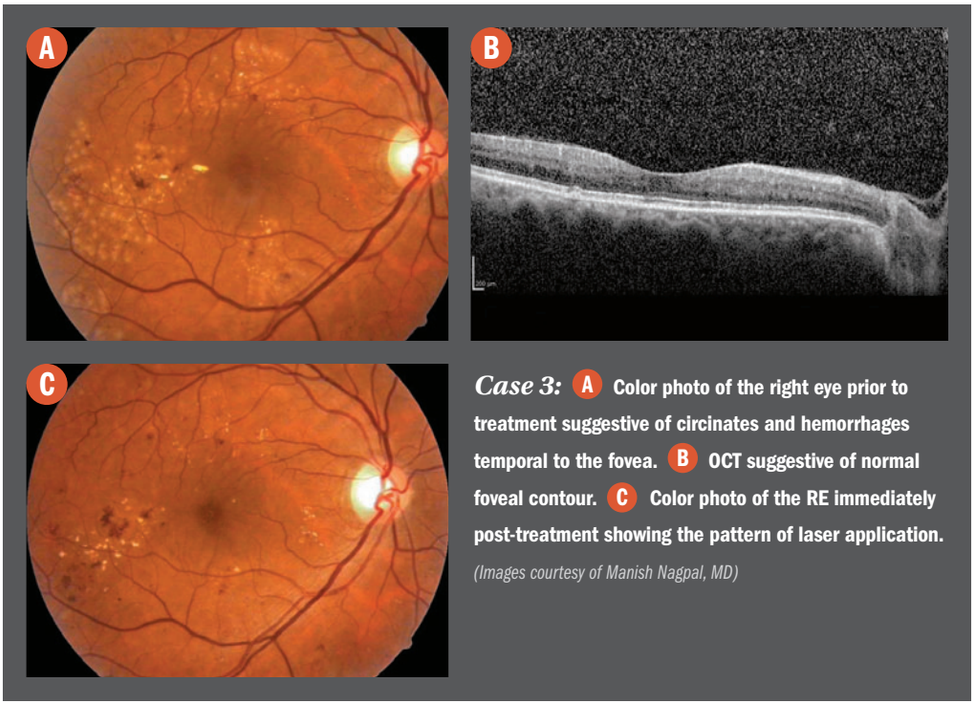
her to return for combination treatments. Grid laser was performed using 100 µm size spots with a 30% setting and 200 mW power. I followed her laser treatment with a ranibizumab injection. At her 1-month follow-up appointment her vision had improved to 20/20 and her edema had regressed significantly.

Case 3: The vision of a 60-year-old diabetic male had been reduced in the month prior to his initial consultation to 20/80. It was determined that he had circinates and hemorrhages temporal to the fovea. I performed an OCT, which revealed a normal foveal contour with no cystoid edema.

In this case I recommended only grid and focal laser treatment. I used the semicircular grid spot burns at 150 mW at a 20-millisecond duration with a 30% to 40% setting. At his 1-month appointment the patient had good regression of his edema and his visual acuity had improved to 20/20. He returned for follow-up appointments for 6 months and his macular edema condition has been stable to date.

In the past, patients have been nervous about receiving injection therapy. As it grows into a more common practice in treating DME, however, patients are becoming more comfortable with this method of treatment.

In any situation, the physician must advise the best possible regimen and utilize the best tools and instruments. As knowledge of lasers and medications advance, we should adjust our treatment protocols accordingly. I have experienced great success with my patients with thoughtful diagnosis and treatment plans, combined with cutting-edge equipment. ■



Case 3: **A Color photo of the right eye prior to treatment suggestive of circinates and hemorrhages temporal to the fovea. B OCT suggestive of normal foveal contour. C Color photo of the RE immediately post-treatment showing the pattern of laser application.**

(Images courtesy of Manish Nagpal, MD)

MANISH NAGPAL, MD, *is based in the Retina Foundation and Eye Research Center, Gujarat, India. Dr. Nagpal is a consultant to Topcon Medical Laser Systems Inc. He may be reached by e-mail at drmanishnagpal@yahoo.com.*

Retinal vein occlusion treatment undergoes paradigm shift with pharmacotherapy

Intravitreal anti-VEGF, dexamethasone may be where to start; protocol may vary with individual patients

By Nancy Groves; *Reviewed by Szilárd Kiss, MD*

NEW YORK ::

A PARADIGM SHIFT in the treatment of retinal vein occlusion (RVO) means that pharmacotherapy has supplanted the concept of watch and wait and the use of laser photocoagulation as first-line therapy, said Szilárd Kiss, MD.

While retina specialists are likely to follow the new recommendations, general ophthalmologists may not be aware of the changes, which would affect their referrals, said Dr. Kiss, a retina specialist and director of clinical research and associate professor of ophthalmology, Weill Cornell Medical College, New York-Presbyterian Hospital, New York.

"Pharmacotherapy with intravitreal anti-vascular endothelial growth factor (VEGF), whether aflibercept (Eylea, Regeneron), ranibizumab (Lucentis, Genentech), or off-label bevacizumab (Avastin, Genentech) or with a steroid—primarily dexamethasone intravitreal implant (Ozurdex, Allergan)—is the standard of care in 2014," Dr. Kiss said.

"There really has been a revolution in the treatment of RVO over the past couple of years," he continued. "Even 3 or 4 years ago, the whole concept of treating RVO was initially watch and wait. If the decreased vision caused by the macular edema secondary to the vein occlusion didn't spontaneously resolve, treatment was initiated, most often with laser photocoagulation in cases of branch occlusion."

UNDERSTANDING THE CHANGES

Over the past couple of years, the results of several large, prospective clinical trials have indicated that watchful waiting does a disservice to patients. In 2014, the concept of sending a patient away without treatment is outdated, and laser photocoagulation is no longer a first-line or possibly even second-line treatment for either branch or central RVO, Dr. Kiss noted.

What all the trials showed was that patients who were treated earlier had a better chance of gaining vision. Under the watch-and-wait protocol, the ultimate visual acuity following treatment was not as good as if patients had been treated earlier. While skeptics might counter that pharmaceutical companies sponsored the trials with a vested interest in positive outcomes for treatment using their medications, Dr. Kiss observed that three different companies conducted the trials, yet produced nearly identical results in terms of earlier treatment (Genentech, BRVO and CRUISE trials; Allergan GENEVA trial; Regeneron GALILEO and COPERNICUS trials).

THE CHANGED PARADIGM

As an example of the changed paradigm, Dr. Kiss would treat patients with BRVO, macular edema, and 20/40 vision with an injection at presentation to his clinic rather than sending them off to wait for the edema to resolve on its own. While anti-VEGF therapy is generally the first choice in pharmacotherapy, this treatment does not work for everyone. In some cases, patients may benefit from switching to a steroid or adjunctive treatment with a steroid.

His threshold for an adjustment in treatment is typically after three injections of anti-VEGF therapy. If optical coherence tomography and vision results are not showing improvement at that point, "I will add a steroid, and that steroid is Ozurdex, to see if A, I can get a better vision result; B, if I can get rid of that fluid; and C, if I can decrease the number of anti-VEGF injections I may need," he said.

Dr. Kiss also cites the work of Michael Singer, MD, of San Antonio, TX, and his colleagues, who showed that combination therapy provides a longer duration of action and perhaps a better result than anti-VEGF therapy alone. (Singer MA, et. al. Effect of combination therapy with bevacizumab and dexamethasone intravitreal implant in patients with retinal vein occlusion. *Retina*. 2012 Jul;32:1289-1294.)

However, laser therapy may be appropriate in a limited number of patients, such as those who develop neovascularization secondary to CRVO or those who have large areas of ischemia typically found on wide-field angiography.

In cases such as a pseudophakic patient presenting with CRVO, it is almost certain that treatment with one or two anti-VEGF injections will be insufficient. To avoid a large treatment burden, Dr. Kiss will instead initiate combination therapy: an anti-VEGF injection on presentation followed a week or two later by a steroid injection.

He also noted that he and other specialists are likely to veer from the treatment regimen followed in clinical trials, due to concerns about the treatment burden of monthly examinations and injections on patients and caregivers–as well as physicians and the healthcare system. While in clinical trials, patients may average 8 or 9 injections in the first 12 months of treatment, the average is closer to 4 in the practice setting.

However, recent research suggests that patients receiving fewer injections are not achieving the same results in visual acuity gains as were found in the clinical trials, Dr. Kiss said. He added, though, that even with fewer injections, results are generally better than the natural history or those resulting from watchful waiting. (Kiss S, et. al. Clinical utilization of anti-vascular endothelial growth-factor agents and patient monitoring in retinal vein occlusion and diabetic macular edema. *Clin Ophthalmol*. 2014 Aug 26;8:1611-1621.)

WORK TOGETHER

"With that being said, injections work, pharmacotherapy works; it's the first line in treatment and works better than waiting," Dr. Kiss said.

He acknowledged that the treatment of retinal disorders is changing quickly, and new paradigms such as that for RVO do not always reach busy practitioners quickly.

His message to the comprehensive ophthalmologist is two-fold: if you see a vein occlusion, make sure that the patient receives a systemic workup with a primary-care physician to ensure that diabetes, hypertension, and underlying coagulopathy are addressed, and secondly, promptly refer the patient to a retina specialist. ■

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Dr. Kiss is a consultant and on the speakers' bureau for Allergan, Genentech, and Regeneron. He receives research funding from all three of these companies, as well as Ophthotech.

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Data: Aflibercept consistent in DME therapy

VISTA-DME/VIVID-DME trials evaluate efficacy of treatment with central involvement, BCVA

By Lynda Charters; Reviewed by Charles C. Wykoff, MD, PhD

HOUSTON :: **INTRAVITREAL AFLIBERCEPT** (Eylea, Regeneron Pharmaceuticals) seems to have similar efficacy in patients with diabetic macular edema (DME) who had been treated previously with anti-vascular endothelial growth factor therapy (VEGF) as in those with DME who were anti-VEGF treatment naïve.

Dr. Wykoff

"Outcomes thus far from the VISTA-DME/VIVID-DME phase III trials indicate the group treated with 2 mg of aflibercept every 8 weeks after 5 monthly doses had similar outcomes to the group treated with 2 mg of aflibercept every 4 weeks, regardless of prior anti-VEGF therapy," said Charles C. Wykoff, MD, PhD.

VISTA-DME/VIVID-DME

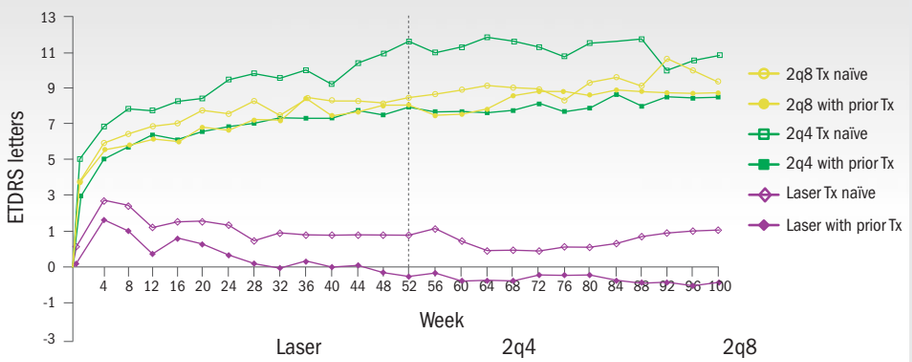
The randomized, multicenter, double-masked trial evaluated the efficacy of intravitreal injections of aflibercept in patients with clinically relevant DME that involved the central macula and BCVA of 20/40 to 20/320. The VISTA segment included 466 U.S. patients, whereas VIVID included 406 patients from outside the United States.

Patients were randomly assigned either to focal macular laser photocoagulation or one of two doses of intravitreal aflibercept: 2 mg every 4 weeks or 2 mg every 8 weeks following 5 consecutive monthly doses, said Dr. Wykoff, who is in private practice, Houston.

Primary endpoint was the mean change in BCVA at 52 weeks. Secondary endpoints included change in central retinal thickness and the Diabetic Retinopathy Severity Score (DRSS) at 52 and 100 weeks. Prior anti-VEGF treatment could have included ranibizumab (Lucentis, Genentech), bevacizumab (Avastin, Genentech), and/or pegaptanib (Macugen, Pfizer/Eyetech).

Analysis of mean changes in BCVA through week 100 indicated two aflibercept arms resulted in similar improvements in visual acuity in patients who were treated previously and in those who were anti-VEGF treatment naïve, with increases of about 11 to 13 ETDRS letters. Concurrent with visual acuity improvements, patients treated with aflibercept experienced decreases in central retinal thicknesses that ranged from about 160 to 190 µm regardless of prior anti-VEGF.

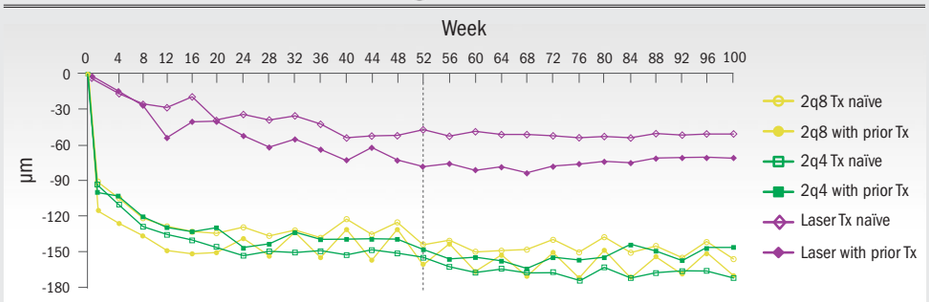
Mean Change in Best-Corrected Visual Acuity Through Week 100



	Laser		2q4		2q8	
	With Prior Tx	Tx Naive	With Prior Tx	Tx Naive	With Prior Tx	Tx Naive
N	63	91	67	87	68	83
Mean Change in BCVA	-0.8	2.1	10.9	12.0	10.8	11.3

Full analysis set; LOCF

Mean Change in Central Retinal Thickness Through Week 100



	Laser		2q4		2q8	
	With Prior Tx	Tx Naive	With Prior Tx	Tx Naive	With Prior Tx	Tx Naive
N	63	91	67	87	68	83
Mean Change in CRT	-94.1	-76.9	-180.1	-200.0	-196.4	-186.7

Full analysis set; LOCF

(Figures courtesy of Charles C. Wykoff, MD, PhD)

At week 100, 35.8% of patients with DME who had received previous anti-VEGF therapy and then 2 mg of aflibercept every 4 weeks had a gain of 15 or more ETDRS letters, as did 29.4% of patients who received 2 mg of aflibercept every 8 weeks following 5 monthly doses.

At week 100, among patients treated previously with anti-VEGF, 15.9% of laser-treated patients, 37.3% of patients treated with 2 mg of aflibercept every 4 weeks, and 38.2% of those treated 2 mg of aflibercept every 8 weeks after 5 monthly doses had an improvement in DRSS of two or more steps. Treatment-naïve patients were 15.4%, 36.8%, and 36.1%, respectively. ■

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This article was based on a presentation by Dr. Wykoff at the 2014 meeting of the American Society of Retina Specialists. Dr. Wykoff is a consultant and speaker for and receives research funding from Alcon Laboratories, Allergan, Genentech, and Regeneron.

Ocriplasmin for VMA: Insights gained

Outcomes data help to guide treatment/management decisions and patient counseling

By Cheryl Guttman Krader; *Reviewed by Jeremy D. Wolfe, MD, MS*

ROYAL OAK, MI ::

FINDINGS FROM A single-center, retrospective review of patients treated for vitreomacular adhesion (VMA) with ocriplasmin (Jetrea, ThromboGenics) add to accumulating evidence demonstrating that appropriate patient selection increases success and also showing that subretinal fluid and ellipsoid zone changes are common, but temporary, post-treatment findings.

"Our data are consistent with a number of other reports showing that the efficacy of ocriplasmin treatment can be high when carefully selecting cases based on optical coherence tomography (OCT) findings shown to be associated with success in the subgroup analyses for MIVI-TRUST," said Jeremy D. Wolfe, MD, MS, Associated Retinal Consultants, Royal Oak, MI.

Dr. Wolfe

"We found the rate of separation was higher in patients with smaller adhesions without an epiretinal membrane, and eyes with VMA and small macular holes appeared to be a particular 'sweet spot' for ocriplasmin treatment," Dr. Wolfe said.

Observations also corroborate findings from after-market reports on early anatomical changes occurring post-treatment, he noted.

"We hope that all of this information should be helpful to clinicians in terms of knowing what to expect when using ocriplasmin and how to counsel patients," Dr. Wolfe said.

The outcomes presented were for all patients treated by Dr. Wolfe and Eric Nudleman, MD, PhD, between February and September 2013. The series included 36 eyes, of which 9 had a stage 2-3 macular hole. Baseline logMAR visual acuity was 0.49 (~20/40).

"As more and more centers are reporting outcomes with ocriplasmin, we were motivated to look at own experience," Dr. Wolfe said.

VMA release at 1 month was analyzed as the primary endpoint, and it was achieved in 15 eyes (42%), including 8 (89%) of the 9 eyes with a macular hole. Macular hole closure was achieved in 7 eyes (78%).

Analyses performed with eyes categorized according to whether separation was achieved showed eyes that separated had a significantly smaller mean adhesion (311 versus 654 µm), and a significantly lower incidence of epiretinal membrane (13% versus 48%).

CHANGES NOTED

Follow-up with post-treatment spectral domain-OCT (SD-OCT) at 1 week showed a higher incidence of subretinal fluid among eyes that separated compared with those that did not (73.3% versus 19%).

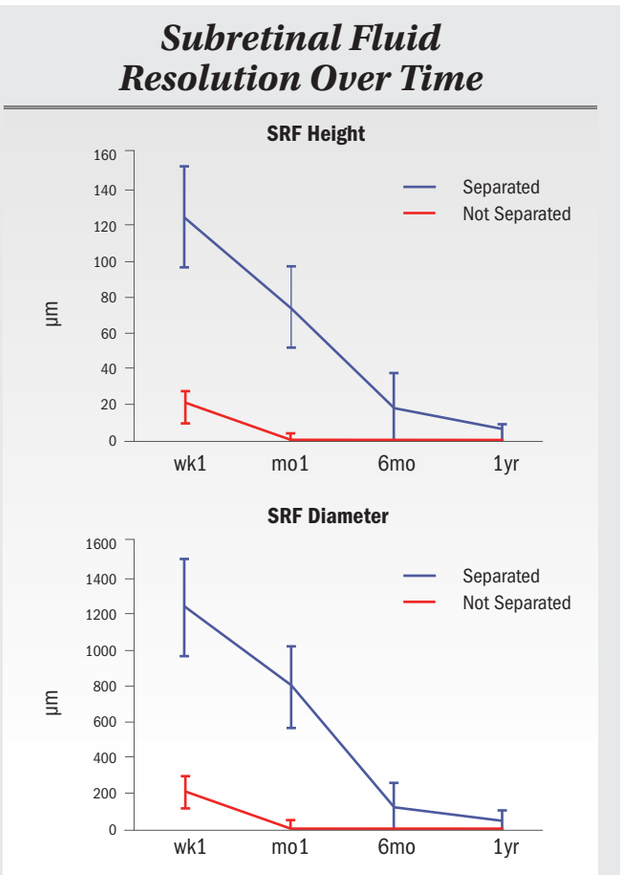
Ellipsoid zone changes—characterized by attenuation of the ellipsoid zone band—were also more common in the group achieving separation (66.7% versus 52.3%), although the difference between groups did not achieve statistical significance.

Findings from serial SD-OCT imaging showed that by 1 month, subretinal fluid had resolved in some patients and mean subretinal fluid height and diameter were each reduced by about half. At 6 months, most changes had resolved. Subretinal fluid persisted at 6 months in 3 patients and improved thereafter in all, but was still present in 2 patients at 1 year.

The ellipsoid zone changes, when present, were also improved at 1 month, and normal anatomy was present in nearly all eyes seen at 6 months, and in all eyes at 1 year.

Visual acuity also continued to improve during follow-up among eyes achieving VMA release. Whereas mean visual acuity was not significantly different between the responders and non-responders to ocriplasmin at 1 month, there was improvement over time in the responder group. At 1 year, eyes that responded to ocriplasmin had a mean gain of 17 letters from baseline best-corrected visual acuity compared with no change in the non-responders, Dr. Wolfe noted.

Safety of ocriplasmin treatment was favorable. There was a single retinal detachment and no cases of severe or persistent vision loss or endophthalmitis. ■



These graphs illustrate both subretinal fluid and ellipsoid zone changes present 1 week after treatment with ocriplasmin, improvement in both subretinal fluid and ellipsoid zone at 1 month, and resolution of both by 6 months. *(Figures courtesy of Jeremy D. Wolfe, MD, MS)*

take-home

- **Analyses of data from patients treated for vitreomacular adhesion at a single center provide insights for management decisions and patient counseling.**

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This article was adapted from the 2014 meeting of the American Society of Retina Specialists. Dr. Wolfe receives research support from ThromboGenics. Dr. Nudleman has no financial interest to disclose.

Genetic testing for AMD takes step in direction of individualized care

Results may affect patients' surveillance regime and treatment recommendations

By Evelyn X. Fu, MD, *Special to* Ophthalmology Times

UNIVERSITY PLACE, WA ::

ADVANCED AGE-RELATED macular degeneration (AMD) is characterized by choroidal neovascularization (64%) and central geographic atrophy (36%).[1] Although advanced AMD impacts only about 10% of the AMD disease population, it accounts for more than 90% of vision loss associated with this condition.[2]

Anti-vascular endothelial growth factor (VEGF) therapies have been proven effective in stabilizing and/or reducing vision loss associated with choroidal neovascularization (CNV) in some patients. Treatment regimes for central geographic atrophy (GA) have shown promising early results.[3]

Therefore, timely diagnosis and treatment of CNV is critical in minimizing the irreversible vision-loss associated with treatment delay.[4-6]

Previously, age, ethnicity, smoking history, and phenotypical characteristics have been the main factors used in identifying patients with high risk of advanced AMD.[7-14]

However, not all patients within a demographic and phenotypic group have the same risk of advanced AMD progression.

For example, a patient with an Age-Related Eye Disease Study (AREDS) Simplified Severity Scale Grade III—which is relatively high risk—may have between a 70% to 90% risk of conversion to wet AMD within 10 years. A different patient with the same grade may only have a 15% to 30% risk of conversion based on genetic influence. (See graph)

Risk assessment purely based on demography and phenotype is limiting and ignores the importance of genetic predisposition.

PRACTICAL TESTING BENEFITS

Selective genotyping allows clinicians to implement individualized surveillance programs that may increase the detection of progression and decrease the burden of unnecessary frequent examinations.

For example, patients who have minimal phenotypical ocular changes (AREDS Simplified Severity Scale Grade I) are often monitored annually or semi-annually.

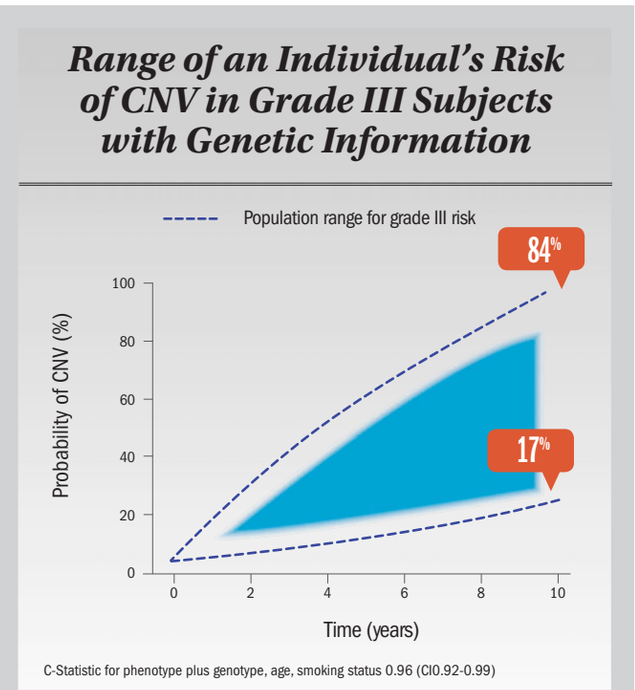
However, patients with high genetic risks may benefit from more frequent examinations. These patients should also be extensively counseled on smoking cessation, weight loss, and healthier diet.

At the same time, they should be started on home vision monitoring programs using the traditional Amsler grid or various commercial applications currently available.

The results from genetic testing can be great motivators for behavior modifications.

On the other hand, patients who have moderate or severe phenotypical changes (AREDS Simplified Severity Scale Grade III and IV) are often monitored very closely—some on a quarterly basis.

These frequent examinations may not be necessary in all of these patients. Surveillance can be tailored in those with low-genetic risks to decrease the burden of frequent visits.



Risk assessment purely based on demography and phenotype is limiting and ignores the importance of genetic predisposition.
(Figure courtesy of Nicox)

PATIENT SELECTION, CONSULTATION

Genetic testing is not warranted in every patient with AMD. I currently consider testing in three groups of patients:

1. **Patients with risky lifestyle behaviors, such as smoking.**
2. **Patients with moderate or severe phenotypic findings (Simplified Severity Scale Grade III or IV).**
3. **Patients with first-degree relatives affected by advanced AMD.**

My approach to recommendation begins with educating patients about the pathogenesis and natural history of AMD. Although phenotyping has been invaluable in assessment, up to 71% of one's risk of advanced AMD is influenced by genetics.[15]

I explain how the results may affect their surveillance regime and treatment recommendations. Patients are provided with extensive reading materials and asked to consider carefully the cost and implications of a laboratory-developed test (RetnaGene, Nicox). If the patient is interested, he or she contacts the practice and schedules a time to undergo testing.

When the patient presents for testing, a technician completes a test requisition form, collects the DNA sample using a buccal swab, places labels on the tube and test requisition form, and prepares the swab for shipping on the same day.

I follow up with the patient 2 weeks after sample submission when the results become available. At this appointment, I explain the testing results, recommend lifestyle changes, and outline a surveillance protocol.

I have found that genetic testing results motivate behavior changes in patients with

OphthalmologyTimes.com
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TIPS FOR MANAGING PIGMENT EPITHELIAL DETACHMENTS WITH RANIBIZUMAB

LARGE OR SMALL pigment epithelial detachments (PED) in neovascular age-related macular degeneration (AMD) can be managed effectively with ranibizumab PRN therapy with regular monitoring, said Rahul N. Khurana, MD. "There is a common belief out there that PED associated with neovascular AMD are quite challenging to manage," he said.
Go to http://bit.ly/1x2Mz2d

poor lifestyle choices and increase compliance with surveillance regimes. Monitoring schedules are implemented based on the patient's individual risk.

Additionally, these encounters are used to educate patients regarding home vision monitoring and to stress the importance of early medical attention with any visual loss.

It is hoped that these efforts will decrease the incidences of patients erroneously attributing visual changes from AMD progression to other unrelated causes, such as cataract or ptosis.

CONCLUSION

Patient selection in genetic testing is crucial. The American Academy of Ophthalmology has recommended against the routine use of genetic screening in AMD.[16]

The utility of genetic screening is particularly limited in asymptomatic patients without known risk factors.

However, directed testing in a subset of the AMD patients with the highest risk of visual loss allow the ophthalmologists to develop individualized management protocols that may motivate behavior modification, increase surveillance compliance, and promote early detection. ■

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Epiretinal prosthesis outcomes remain encouraging for retinitis pigmentosa

Increased mobility, orientation, object identification improve patients' quality of life

By Cheryl Guttman Krader; *Reviewed by Stanislao Rizzo, MD*

PISA, ITALY ::

IN ONGOING follow-up now extending to 3 years, an epiretinal prosthesis (Argus II Retinal Prosthesis System, Second Sight Medical Products) remains well tolerated and continues to provide patients with benefits of improved visual function and quality of life, said Stanislao Rizzo, MD.

Dr. Rizzo was the first surgeon in the world to implant the retinal prosthesis after it became commercially available. That was in October 2011, and his series now includes 12 patients blind from retinitis pigmentosa. All had no light perception vision at the time of implantation and they ranged in age from 30 to 65 years.

During follow-up of 12 to 32 months, there have been no serious complications related to the surgery or the device. Patient feedback and results from formal testing show the recipients have maintained improvements in mobility, orientation, and object identification. In addition, Goldmann visual field testing improved in all patients, and one patient achieved grating visual acuity.

QUALITY OF LIFE

While those outcomes are amazing, even more important is the tremendous positive impact the implant has had on quality of life, said Dr. Rizzo, director, U.O. Chirurgia Oftalmica, Ospedale Cisanello, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy.

"We have shown the benefits of the retinal prosthesis using validated quality-of-life instruments," Dr. Rizzo said. "However, the spontaneous comments of patients, who for example are thrilled to be able to recognize family members for the first time in many years, tell an even more compelling story.

"Clearly, the [retinal prosthesis] is a revolutionary advance for improving the lives of patients with a very debilitating disease, but we expect it is just the beginning as the technology improves and new systems are developed," he said. "The Argus II is already the second generation of the epiretinal prosthesis, and there have also been numerous upgrades to its software and some of its hardware components."

The system comprises a video camera mounted on a pair of glasses, an externally worn video processing unit (VPU), an inductive coil (antenna) fixed on the sclera, and a 60-electrode epiretinal array that is implanted onto the macula via a pars plana approach. The camera receives visual input that is converted to a stimulation pattern by the VPU. The VPU transmits the data and power wirelessly to the antenna that is hardwired to the epiretinal array.

When the information is transferred to the array, it stimulates the viable retinal neurons below the photoreceptors (bipolar and ganglion cells). Their signal is relayed to the visual cortex via the optic nerve.

Dr. Rizzo said that the implantation surgery is not that technically difficult for skilled vitreoretinal surgeons. However, it is long and involves some novel elements both within and outside of the posterior segment, such as for fixation of the epiretinal array to the macula and of the antenna to the sclera.

"Surgeons who perform the implantation need to be a 'complete' surgeon, and they need to know that relative to familiar operations, it is an arduous procedure," he said.

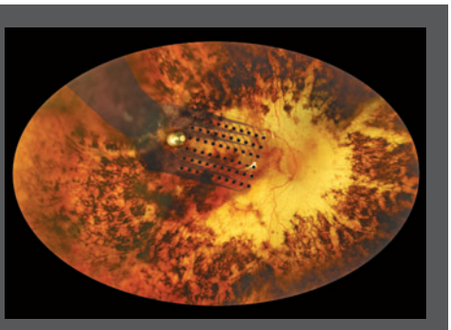
"However, the surgical time is significantly reduced after passing the learning curve," Dr. Rizzo said. "While our first procedure took 4 hours to complete, in later cases we finished the implantation in less than 2 hours."

Dr. Rizzo said the prosthesis was safely implanted in all 12 patients. Postoperative complications included elevated IOP in one patient, which was controlled with topical medication, and a moderate detachment of the choroid in one patient, which resolved spontaneously.

"Patient safety is always paramount, and so it is important to note that the device appears to be highly biocompatible and there have been no real concerns for implanted patients," Dr. Rizzo said.

CHOOSING CANDIDATES

Dr. Rizzo said that careful patient selection is critical when choosing recipients for the prosthesis, and there are a variety of issues to consider. Eligible patients are those with severe outer retinal degeneration, but with surviving inner retinal cells and ganglion cells able to respond to the electrical stimulation. As another anatomic requirement, axial length must be between 22.5 and 27 mm because the cable running from the array to the antenna is a fixed length.



Electrode array as it is positioned on the retina.
(Image courtesy of Second Sight Medical Products Inc.)

Patients also have to be in good general health because the lengthy procedure is done under general anesthesia. In addition, they need to have appropriate expectations for outcomes, and they and their families must be judged as being motivated to reliably comply with the intense rehabilitation process.

"Patients need to understand and accept that the prosthesis provides a limited form of vision, and this is discussed at length and several times in the preoperative consultations," Dr. Rizzo said.

"After the surgery, patients need to learn a new form of vision that is completely different from natural vision," he said. "The outcome . . . depends not only on the success of surgery, but also on the patient's participation in the rehabilitation training program." ■

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This article was adapted from Dr. Rizzo's presentation during Retina Subspecialty Day at the 2014 meeting of the American Academy of Ophthalmology. Dr. Rizzo has no relevant financial interests to disclose.

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MICROPUMP

(Continued from page 1)

Humayun, adding that noncompliance issues result in almost $300 billion of direct and indirect medical costs yearly in the United States. This version of the device is smaller than the one designed for glaucoma, but it has a larger reservoir volume.

As a result, the pump is refilled via a 31-gauge needle. The device also has a separate console unit that is used to fill and refill the implant.

Dr. Humayun

"The pump has been shown to be capable of use for more than 7 years and further longevity tests are ongoing to determine how much longer it can work," Dr. Humayun said.

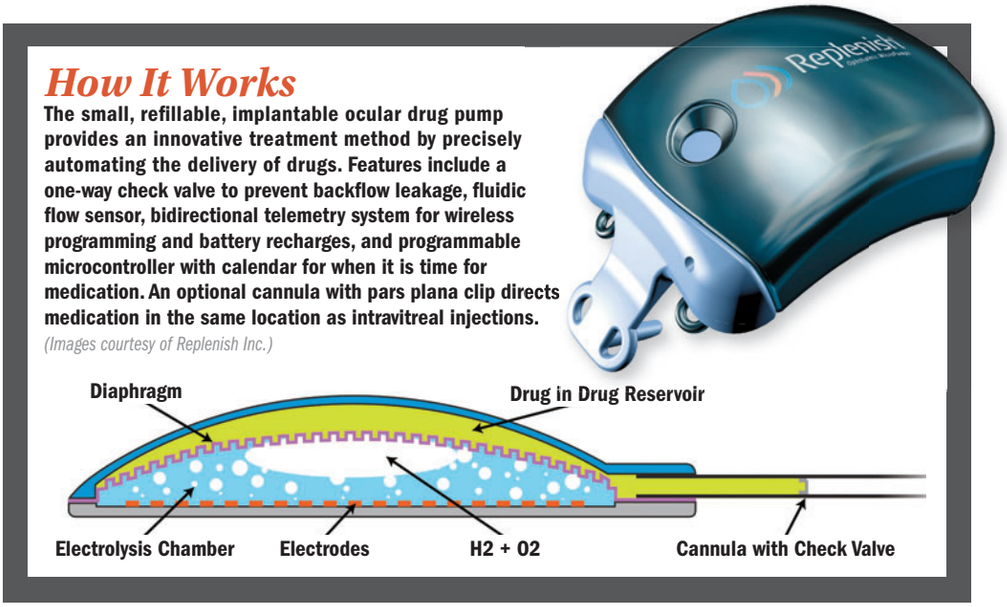
The reservoir can be replenished within 2 minutes in the clinic, he added, thus alleviating some of the pressure of increased patient loads.

"This marks a new direction in ocular bioelectronics devices, and our second-generation [micropump] can hold up to 100 microliters," he said. "This device has a lot of potential, with multiple chambers for different drug delivery."

As with most novel devices, Dr. Humayun said, "additional clinical studies are required to further validate our findings, but controlled drug delivery via this pump for chronic diseases of the retina is feasible."

FIRST LOOK AT RESEARCH

Eleven subjects with DME and visual acuity of logMAR 0.30 or worse were included in the initial study for the pump. The device, filled with ranibizumab, was implanted using similar techniques used for implanting a glaucoma drainage device.



After implantation, the device was wirelessly controlled to deliver a preprogrammed dosage of ranibizumab.

Comprehensive ophthalmic examinations and optical coherence tomography were performed biweekly for 90 days. At day 90, the device was explanted and the subjects thereafter received standard of care.

No serious adverse events were reported after 90 days. All subjects exhibited a normal course of healing. One patient had a small vitreous hemorrhage from the sclerotomy site at week 1, which did not cause a decrease in visual acuity and was resorbed at postoperative week 4.

"There were no reported instances of foreign body sensation," Dr. Humayun added. "Transient diplopia only elicited in extreme gaze positions was minimal and resolved completely within 6 weeks postoperatively."

Out of the 11 subjects, the micropump device delivered the preprogrammed dosage within 20% of target in seven subjects. For the successful seven subjects, there was an improvement in visual acuity and retinal thickness at day 28 compared with baseline.

In four subjects, the device had a slower rate of delivery than desirable clinically, and the team decided to complete the dosing regiment using intravitreal injection.

Of the four unsuccessful attempts, the pump itself was damaged during implantation in one case, and in the other three cases, the pump was unable to deliver the dose within the allotted time, Dr. Humayun said. Improvements are being made for the next study.

No subject had loss of visual acuity during the study.

The device is for investigational use only and not yet approved for commercial distribution. ■

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This article was adapted from Dr. Humayun's presentation at the 2014 meeting of the American Society of Retina Specialists. Dr. Humayun is inventor of the technology and co-founder of Replenish Inc.

Health Canada OKs ranibizumab for CNV

By Rose Schneider

DORVAL, QUEBEC, CANADA ::

HEALTH CANADA has approved Novartis Pharmaceuticals Canada's ranibizumab (Lucentis) for the treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (mCNV).

Treatment of vision loss from mCNV with ranibizumab starts with a single injection, with further injections as needed based on disease activity, which is monitored monthly for the first 2 months then at least quarterly for up to 1 year. After the first year, frequency of monitoring is at the discretion of the treating physician.

The phase III study on which the approval of the new indication was based, showed that treatment with ranibizumab was superior to the previous standard of care, verteporfin photodynamic therapy (Visudyne).

Ranibizumab improved mean visual acuity by about 14 letters (on an eye chart) after 1 year. This result was achieved with a median of two injections over the 12 months.

More than 60% of patients in the trial did not need any further injections after 6 months, according to a prepared statement from the company.

Previous treatments for mCNV aimed to stabilize vision but generally did not improve visual acuity, the company said. ■

Continuous steroid therapy may help those with chronic DME, worst vision

Earlier intervention improved likelihood of achieving good final visual outcome, data suggest

By Cheryl Guttman Krader; *Reviewed by Usha Chakravarthy, MD*

BELFAST, NORTHERN IRELAND ::

FINDINGS FROM exploratory analyses of visual outcomes data in the Fluocinolone Acetonide in Diabetic Macular Edema (FAME) study highlight that continuous, low-dose steroid therapy with the fluocinolone acetonide implant (Iluvien, Alimera Sciences) has particular benefit for patients with chronic DME versus laser and intermittent intravitreal steroid and anti-VEGF therapy.

In addition, the data show the likelihood of achieving a good final visual outcome (BCVA of 20/40 or better) is improved with earlier intervention and this effect is further improved by intervention with continuous, low-dose steroid therapy, said Usha Chakravarthy, MD, PhD, professor of ophthalmology and vision sciences, The Queen's University of Belfast, Northern Ireland.

Dr. Chakravarthy

The FAME study program randomly assigned 956 patients with DME into three arms (2:2:1) to receive the fluocinolone acetonide (FA) implant 0.2 mcg/d (approved dose), FA implant 0.5 mcg/d, or sham control. Eligible patients had at least 1 previous laser treatment to the study eye, a BCVA (ETDRS letter score) between 19 and 68 letters, and center point thickness ≥ 250 µm.

All patients could receive rescue laser 6 weeks after randomization at the discretion of the investigator who was masked to treatment assignment and re-treatment with the randomized therapy at 12 months if they met pre-specified criteria (BCVA loss ≥5 letters or increase in center point thickness ≥50 µm from the best reading in the previous 12 months).

Dr. Chakravarthy reported results of subgroup analyses [all baseline BCVA, BCVA ≤63 (20/64), 58 (20/80) and 53 (20/100) letters] looking at proportions of patients whose BCVA at month 36 was improved ≥15 letters from baseline or was 20/40 or better. Comparisons were made between chronic and non-chronic DME patients treated with the FA implant 0.2 mcg/d group (n = 375) and the control group (intermittent therapy) (n = 185). Within both of those treatment arms, the majority of patients had chronic DME (55.7% and 60.5%, respectively).

The data showed a significantly larger treatment benefit (greater proportion of 15-letter gainers) in the FA implant group than the controls. The difference favoring continuous low-dose steroid therapy over intermittent therapy was more apparent when analysis was restricted to patients with chronic DME and was also seen when the two treatment groups were compared with chronic DME patients stratified into three subgroups by baseline vision.

Considering only patients with chronic DME treated with FA 0.2 mcg/d, the proportions of patients who achieved a ≥15 letter improvement from baseline BCVA at month 36 increased with worsening BCVA: 38.5%, 42.7%, and 46.7%, respectively. However, in the sham patients with chronic DME, the proportion of patients with a ≥15-letter improvement in BCVA at month 36 decreased as baseline BCVA worsened: 14.4%, 12.7%, and 12.5%, respectively.

The treatment differences comparing the FA implant and control groups increased as baseline visual function worsened (24.1%, 30.0%, and 34.2%), and the treatment differences were all highly statistically significant (p <0.001).

SUBSEQUENT ANALYSIS

To understand why control patients were not exhibiting the same profile in terms of vision improvement as patients treated with the FA implant, a subsequent analysis focused on the control patients stratified by disease chronicity.

Results showed patients with chronic DME did not respond well to intermittent therapies. Segregating sham groups by DME chronicity and by baseline BCVA strata showed the proportion of patients gaining ≥15 letters from baseline BCVA was similarly poor regardless of baseline BCVA for the sham-treated patients with chronic DME (12.5% to 14.4%). These results were in contrast to outcomes observed in the sham patients with non-chronic DME that showed better response to intermittent therapies overall, with an increasing proportion of ≥15-letter gainers across strata of worsening baseline vision (≤20/64 = 32.7%; ≤20/80 = 42.4%; ≤20/100 = 50.0%).

"We also investigated why the control patients were not exhibiting the same profile as those receiving the FA implant by looking to see if there were any differences between chronic and non-chronic DME control patients in receipt of off-protocol treatments (intravitreal injections of triamcinolone and anti-VEGF agents), laser photocoagulation, or sham injection," Dr. Chakravarthy said.

"However, the two subgroups of control patients were treated very similarly," she said. "This difference in response . . . is indicative of the difference in the microenvironment of the retina of chronic versus non-chronic DME patients."

Another analysis investigated how DME chronicity affected the ability to achieve a BCVA of 20/40 at month 36. When the chronic control population was compared with the non-chronic control population, a difference emerged in terms of the proportion of patients achieving a BCVA of 20/40 or better. With worse baseline BCVA and intermittent therapies, the chronic DME patients had a lower chance of achieving BCVA of 20/40 or better.

When this comparison was made between the FA implant-treated chronic and non-chronic populations, the difference in chance of achieving a BCVA of 20/40 or better was not apparent. Treatment with the implant seemed to normalize the chronic DME patients to respond more like the non-chronic patients. ■

take-home

▸ Exploratory analyses of FAME study data reinforce benefits of continuous low-dose steroid therapy and suggest that earlier intervention improved the likelihood of achieving a good final visual outcome.

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Dr. Chakravarthy received honoraria for attendance at advisory boards for Alimera, Bayer, Novartis, and Roche and support for travel for attendance at scientific meetings.

Innovation in glaucoma thriving

Advances in pharmaceuticals, devices, and diagnostics fueling growth for sector

By Fred Gebhart; *Reviewed by Emmett Cunningham Jr., MD, PhD, MPH*

SOUTH SAN FRANCISCO, CA ::

Innovation in glaucoma diagnosis and treatment is alive and well. The glaucoma pharmaceutical sector alone is set to grow from $4 billion in 2013 to $5 billion by 2018, according to Emmett Cunningham Jr., MD, PhD, MPH.

"The glaucoma market is growing very nicely," said Dr. Cunningham, partner with venture capital firm Clarus Ventures LLC. "We are not seeing any slowing of innovation in glaucoma."

APPROVAL, PIPELINE PROGRESS

The approval of Alcon Laboratories' combination drug of brinzolamide and brimonidine (Simbrinza) is the first fixed-dose, combination glaucoma agent without a beta-blocker to be approved for the U.S. market, Dr. Cunningham noted. The net IOP lowering achieved with the agent at various time points suggests FDA flexibility regarding approval thresholds, he said.

The drug pipeline is equally promising. Amakem Therapeutics presented early clinical results for AMA0076, a topical Rho Kinase inhibitor (ROCKi) with activity confined to the anterior chamber. Seven-day data in normotensive eyes showed what Dr. Cunningham called a "very nice" IOP-lowering effect that is greater than reductions usually seen in normotensive eyes. Because activity is localized, there appeared to be less redness than has been seen with other ROCKi agents, he noted.

A multiple dose-parallel-group study of AMA0076 in patients with primary open-angle glaucoma or ocular gypertension is ongoing.

With AR-13324—a combination ROCKi and norepinephrine transport inhibitor (NETi) from Aerie Pharmaceuticals—the ROCKi facilitates outflow whereas the NETi decreases aqueous production. Phase IIb data for a full cohort of 221 eyes with once-daily dosing showed IOP lowering that is about <1 mm Hg than latanoprost. A subgroup analysis of patients with a baseline IOP of between 22 to 26 mm Hg showed clinically and statistically equivalent lowering of IOP, compared with latanoprost at 14 days and 28 days.

"That is an important finding because most glaucoma patients fall into that 22 to 26 mm Hg range before treatment," Dr. Cunningham said. "At the same time, the phase I pharmacokinetics study showed a 30% reduction in IOP for normotensive eyes, which is better than the IOP reduction seen with prostaglandins. The results suggest a novel mechanism of action."

Dr. Cunningham

ROCKi agents act through the trabecular meshwork to facilitate outflow, but the precise mechanism is not entirely clear. It is known that outflow resistance is a major determinant of IOP. Outflow resistance is determined in large part by the episcleral venous pressure (EVP). EVP sets an effective floor for IOP, which suggests that Aerie's ROCKi agent may act by reducing EVP, he noted.

"ROCKi agents hold major promise," Dr. Cunningham said. "They offer significant IOP reduction through the range of pressures we see in practice, not just at the high end."

DEVICE WORLD

Glaucoma devices are starting their own growth spiral, Dr. Cunningham noted. Glaucoma procedures account for about 5% of the 46 million ophthalmic procedures performed globally each year. Microinvasive glaucoma surgery (MIGS) came on the scene in 2012 and is set to surpass traditional glaucoma surgeries by 2016.

Traditional shunt and filtering surgery numbers have been virtually flat the past 2 or 3 years, he said. Nearly all the growth in glaucoma procedures has come from MIGS.

"Glaukos founded the MIGS space in 2012 with the iStent," Dr. Cunningham said. "In 2013, they did over $20 million in revenue, which is fantastic for a first full year on the market."

Glaukos continues to grow, he continued, but the company will not have the market to itself for long. Several competitors are moving through clinical development toward what they hope will be approval, including Transcend Medical (CyPass Micro-Stent), AqueSys (XEN Gel Stent), and Ivantis (Hydrus Microstent).

DRUG DELIVERY

Drug delivery is a weak point in glaucoma treatment, Dr. Cunningham said. Eye drops work, but only if used properly. Adherence falls well below 50% for most topical glaucoma agents within the first 6 months.

"Developing sustained-release drug delivery is important," he said. "Punctal plugs have moved into phase II trials with latanoprost."

What began as a 1.45-mm punctal plug from ForSight has moved to QLT to Mati Therapeutics. The initial design has been re-engineered so that the plug is better retained in the punctum.

Ocular Therapeutix is moving forward with its punctal plug with travoprost. The company is evaluating a 3-month formulation for sustained-release travoprost in a randomized, parallel-arm study, and entered phase II trials this year.

DIAGNOSTICS

The latest development in diagnostics includes devices for continuous monitoring. Two designs are moving through development.

Sensimed's Triggerfish is an external device that provides continuous IOP measurement.

Implandata Ophthalmic Products is developing a permanent device to be implanted during cataract surgery. IOP data are transmitted to an external unit, using an RFID-powered system originally used in automotive applications.

"These are both promising products, given that more data is always better," Dr. Cunningham said. "The major unanswered question is who will pay for such data, and whether outcomes data will need to be generated to convince payers." ■

Editor's Note: *This article was adapted from Dr. Cunningham's presentation during Glaucoma 360° held in association with the Glaucoma Research Foundation and* Ophthalmology Times. *For the latest study updates, visit* www.clinicaltrials.gov.

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Providers navigate effects of ACA with steps for increased efficiency

First year of 'Obamacare' brings vision benefits for children, challenges for practices

By Liz Meszaros

Negotiating the twists and turns inherent to the new health-care reform act can be tricky, said Terri Pickering, MD. In order to succeed, ophthalmologists must remain aware of and ready for inevitable changes.

The Patient Protection and Affordable Care Act (PPACA)—commonly called the Affordable Care Act (ACA) and "Obamacare"—was signed into law March 23, 2010.

"It is the most sweeping regulatory overhaul of the U.S. health-care system since the passage of Medicare and Medicaid in 1965," said Dr. Pickering, who is in private practice at the Glaucoma Center of San Francisco. "It is so sweeping that it is predicted [more than] 1 million people will actually give up the jobs that they hate and are only hanging on to get health care by 2021."

Among the initiatives that the ACA has set to achieve are to:

- Increase the quality and affordability of health insurance;
- Reduce the number of uninsured by expanding public and private insurance coverage;
- Reduce health-care costs for individuals and the government via accountable care organizations (ACOs);
- Reduce the number of medical bankruptcies (the leading cause of bankruptcy in the United States).

TAKE-HOME

- *Terri Pickering, MD, highights some of the uncertainties and issues that surrounded the first year of implementation for the Affordable Care Act with regard to ophthalmology.*

CHILDREN SEE BENEFITS

Benefits also extend to younger patients. In 2005, it was estimated that there were about 9 million uninsured children. Vision benefits are extended to all children up to 19 years old, and parents will no longer need to avoid getting a child's vision checked or corrected due to cost concerns. ("How children benefit from 'Obamacare,' " *Ophthalmology Times*, Nov. 1, 2013, Page 30; *http://bit.ly/1hsC9SS*)

"The biggest benefit that we can see, especially from ophthalmology, is to children," Dr. Pickering said. "Pediatric vision services have been designated one of the 10 essential health benefits, and this is really beneficial for youth."

SHIFTING THE BURDEN OF COST

At one point in the health-care exchange enrollment period, there were about 6 million enrollees, with a high number of Latinos and African-Americans. About 80% of enrollees chose bronze or silver plans with higher, out-of-pocket expenses.

"These may give fewer expenses to the insurers, but may be a higher burden and a barrier to health care for patients," Dr. Pickering said.

In addition, concerns arose over the low numbers of young adults who were signing up. The goal is that 40% of enrollees should be between ages 18 and 34 years, and only 24% were enrolling initially.

"This has caused some of the insurers to take a step back," Dr. Pickering said. "The insurers say they want quality care, but in reality, they really want low-unit costs."

One of the reasons costs for Obamacare are shifting is that—unlike individuals and unlike physician practices—the insurers have a bailout, which is why they signed on to participate in this plan in the first place, she said. It is written within the law and for some of them, may be upward of $450 million.

"This has led to some pessimism regarding this law, that it may be just a very costly entitlement plan, adding layers of bureaucracy," Dr. Pickering said.

"Ultimately, for patients, our concern is that it's low-quality insurance, which may lead to patients having difficulty finding doctors who will even accept these plans," she said.

In California, for example, enrollees hit snags where the insurer websites say they have a certain panel of physicians. When the patients go to these physicians, the physicians tell them "no," that they haven't agreed to participate in that network.

Insurers have shifted the financial burden imposed by the ACA from themselves to patients and physicians, not just in terms of high deductibles, but also in cutting physicians from

Continues on page 52 : **Providing care**

Increasing efficiencies: Staying one step ahead

TERRI PICKERING, MD, shared some suggestions to help ophthalmologists accomplish this:

- Reduce office bottlenecks.
- Streamline lanes for an ideal ratio of 3 lanes:1 ophthalmologist.
- Use electronic health records to reduce no-show rates, length of time until next available appointment, and patient time in the office.
- Be proactive with brochures.
- Consider the possibility of home or remote disease monitoring.
- Do not try to work faster to increase efficiency. This will only increase mistakes.
- Delegate to technicians for a 2:1 ratio.
- Cross-train technicians.
- Optimize optometrists' productivity.
- Constantly communicate from the top down and the bottom up.
- Create an integrated eye-care team, in which optometrists, assistants, and staff support the ophthalmologist in assessing data, diagnosis, and counseling patients.
- Be open to new ideas and remember the power of incremental advantage. ■

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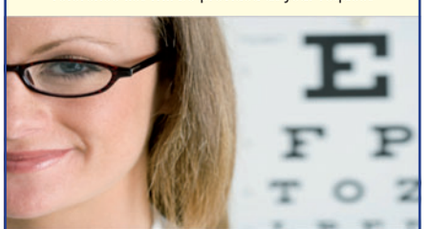

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Interested individuals should submit their curriculum vitae with a cover letter and contact information for four references electronically to Brian Kim, MD at Brian.Kim@vtmednet.org or apply on-line at https://www.uvmjobs.com

PROVIDING CARE

(Continued from page 46)

networks and limiting panels available to patients, she noted.

"This all has created a perfect storm for us," Dr. Pickering said. "In looking forward to our practices as ophthalmologists, what we can predict is more pediatric patients but also more adult patients.

"Regardless of how many people sign up for Obamacare, it will add on to the increased burden presented by the Baby Boomers," she said.

Further possibilities include:

- **The Patient-Centered Outcomes Institute will give new guidelines to ophthalmologists.**
- **Ophthalmologists will be working closely with primary-care physicians.**
- **Electronic health records will be a big issue.**
- **Practice mergers will occur. "The ACA favors ACOs and large interdisciplinary provider structures, which will inevitably lower costs per-unit patient," Dr. Pickering said. "This factor—including the increasing cost of medical technology and malpractice insurance—means private, single practice will become a vanishing entity. Some predict that 75% of physicians will be employed by health-care systems in the next decade."**
- **ASCs may become more attractive to hospitals.**
- **Reimbursements will drop, especially for specialists. Payment plans are changing, moving toward more bundled payments and less fee-for-service.**

MEDICARE VIGILANCE

Medicare is another big feature. In 2010, ophthalmic services accounted for about $6.8 billion for Medicare, and now the ACA has placed an enormous emphasis on Medicare fraud.

"These two factors mean that for the first time, ophthalmology will be targeted by the Office of the Inspector General for fraud investigations," Dr. Pickering said. "Once you get on that listing, you basically never get off."

Medicare is also training 2 million senior citizens to report fraudulent billing. There will be more fraud investigations and more government penalties.

Another factor that will be huge for ophthalmologists is the rise of mid-level practitioners. This is now occurring because there is a shortage of physicians and nurses throughout the country.

"The Department of Health and Human Services and state legislators tend to regulate health care willy-nilly," Dr. Pickering explained. "They have to fill a gap in care; they have to provide services; and they just put bodies in to do the care. There is no consensus across the country as what an optometrist, a nurse practitioner, or a physician's assistant can do versus and MD or an RN."

In particular, nurse practitioners and optometrists are moving to increase their scope of practice to include surgery.

'PERFECT STORM'

"How do we stay afloat in this perfect storm?" Dr. Pickering posited. "The reality is that we have to increase our patient efficiency. It is important to define medical efficiency as maintaining or developing high-quality care in the shortest amount of time, but without accepting unnecessary risks."

SERVING GREATER POPULATION OF PATIENTS

The American Academy of Ophthalmology (AAO) is helping as well, with the creation of the IRIS Registry.

Additionally, the AAO and the American Academy of Optometry have discussed a joint educational initiative. The goal is to prepare for the delivery of the highest quality eye care and to foster a mutual approach to serve the growing population of patients expected in the near future.

"We have to take care of more people," Dr. Pickering said. "We also have to take better care of more patients and provide care for an expanding population.

"We are in the midst of a health-care revolution, which is really a continued re-invention of the American health-care system," she concluded. "The interesting thing is that this [reform] is changing as we speak, and the end product has yet to be determined. Stay tuned! And remember, anything can happen." ■

Editor's Note: *This article was adapted from Dr. Pickering's presentation at the Glaucoma 360° meeting held in association with the Glaucoma Research Foundation and* Ophthalmology Times.

ACA earns higher scores with physicians

By Donna Marbury

PHYSICIANS ARE FEELING more positive about the Affordable Care Act (ACA) this year compared with 2013, according to a new survey by the Medicus Firm.

More physicians give health-care reform an "A" overall—8.6% this year compared with 6.3% last year. Also, fewer physicians see the ACA as a failure. About 30% graded the ACA with an "F" in 2013, compared with 22% in 2014.

More than 2,200 physicians in 19 specialties from all 50 states answered detailed questions about the ACA, grading on an A through F scale.

When it comes to improving access to healthcare, 23% of physicians gave the ACA an "A" and 27% gave it a "B." Nearly 14% of physicians said the ACA failed at improving access to health care—24% of physicians gave the ACA an F in that category last year. Only 7% of physicians gave the ACA an "A" for improving efficiency of health care, while nearly 30% say the ACA is failing in that area.

The survey took place several months after the launch of the health-care exchanges in October 2013. Analysts have questioned how the ACA would affect physicians since its inception 4 years ago. There have been positives, including more patients with insurance coverage and mandatory coverage of preventive health screenings, which ultimately brings more people into practices. However, an increase in the number of patients purchasing high-deductible plans and the possibility of new patients overwhelming already-busy practices. Also, the 90-day grace periods mandated with new health plans could cause practice owners to have to collect payments from patients who don't pay their premiums.

"The ACA has been a game-changer for many physicians' careers," said Jim Stone, president of the Medicus Firm. "Not only are their careers and daily lives significantly impacted by this law, physicians are also on the front lines, seeing the effects of the ACA on patients, physicians, and the health-care industry—for better or for worse." ■

How employing optometrists may bring measurable benefit; ease practice burden

Integrated eye-care delivery: Adding optometry and physician extenders to the clinic

By Stephanie Skernivitz

STILLWATER, MN ::

AS THE U.S. population continues to age, the demand for more eye care for older patients is ever increasing. Yet, the supply of ophthalmologist time is shrinking, leading to a shortage of available eye-care professionals.

"How will we provide the integrated eye care that this group needs?" asked Stephen S. Lane, MD, adjunct clinical professor, University of Minnesota, and medical director, Associated Eye Care, Stillwater, MN.

Dr. Lane

In an impromptu poll of an audience at a recent ophthalmic meeting, he asked: "Do you currently employ optometrists in your office?" Sixty-four percent answered "yes." When asked how optometrists were used in the practice, 22% said as physician extenders, 55% said as independent comprehensive practice within the practice, 18% reported their use as a technician, and 5% had "other" reasons.

For those who answered "no" to employing optometrists in practice, they were asked: "Why not?" The answers: too expensive (5%); opposed to the concept (10%); would not fit current practice style (33%); may interfere with co-management already in place (10%); or planned to employ one in future (43%). No doubt, there is an ever-expanding number of Baby Boomers who are reaching a retirement age of 65 years every day—to the tune of 10,000 per day for the next 17 years.

"We better figure out how it is that we're going to take care of all these patients in our practice," Dr. Lane said. Commercially, in the 16- to 65-years age groups—about 74 cents is being spent per person on care. For seniors over 65 years of age that number jumps to $6.52—8.8 times as much money.

CONSIDER OD'S ROLE

What role should optometry play in this increasing need for eye care? he asked. Currently, there is an ophthalmologist-only eye-care delivery model, as well as an ophthalmologist/optometrist cooperation model. Now what is gaining more attention is what is referred to as an integrated eye-care delivery model.

In these above-mentioned optometric relationship models, the question is how do ophthalmologists perceive optometrists?

"Some perceive them internally as a super-tech/screener, some as a colleague," Dr. Lane said. "From an external standpoint, that is, optometrists outside your practice, (some perceive) these folks as interlopers, referral sources, and colleagues."

As Dr. Lane explained, internally, for internal optometry models, the super-tech/screener is essentially one who works up patients for the ophthalmologist to finish, such as fitting contact lenses, and providing some postoperative exams, but few exams on their own.

"This is a fairly expensive model for the [ophthalmologist] practice to take on compared with using techs only for work up," Dr. Lane said.

BREAKING DOWN THE MODEL

In the internal models where optometrists are treated essentially as a colleague, it is often typical, according to Dr. Lane, for the optometrist to see patients with routine needs; the optometrist practices to the limit of licensure and training, and the optometrist refers medical and surgical patients to the ophthalmologist. In reverse, the ophthalmologist refers patients to the optometrist for routine, postoperative care, contact lenses, and other exams, which optimizes the time spent for the ophthalmologist and optometrist and allows the existing ophthalmologist to do more surgery as opposed to adding another ophthalmologist.

"This model can be more cost effective," Dr. Lane said.

In delegation models, this is where some elements of exams and most ancillary testing are delegated to employees. Most clinical employees are not licensed, though some are certified.

"But there is shortage of trained techs, which forces many practices to train their own," Dr. Lane said.

Overall, Dr. Lane said there is minimal use of physician assistants and nurse practitioners.

How can practices evaluate themselves and determine whether to change models?

Stephen S. Lane, MD suggests that physicians truly ask some probing questions:

1) IS THE DEMAND FOR YOUR SERVICES GREATER THAN THE SUPPLY OF TIME?

Determine whether the lead time to get an appointment is greater than 2 weeks and growing. Are there long patient waiting times? Are you working beyond scheduled hours? Is the ophthalmologist performing a high volume of routine exams?

"If extra help is added, but patient flow doesn't increase, the cost of extra help is simply a drain on practice resources. But on the other hand, if you maximize the use of these folks, the profitability of the practice increases," Dr. Lane said.

2) WHEN DECIDING WHETHER TO CHANGE MODELS, YOU HAVE TO ASK: IS THERE ENOUGH PATIENT DEMAND TO INCREASE THE PATIENT FLOW ENOUGH TO PAY FOR INCREASED COSTS?

3) WHAT IS THE LONG-TERM PLAN OF THE PRACTICE?

4) AT WHAT PACE DOES THE OPHTHALMOLOGIST WORK? WILL THAT PACE BE COMPATIBLE WITH A NEW MODEL?

5) IS THE PRACTICE CAPABLE OF HANDLING ADDITIONAL MANAGEMENT?

"It's an opportunity to provide education to optometrists and physician extenders to improve quality of care and efficiency available," Dr. Lane said. ■

At present, the average comprehensive ophthalmologist sees about 44 patients per day; retina specialists may see about 29 patients a day; pediatric ophthalmologists may see 30;

Continues on page 54 : ***integrated***

INTEGRATED

(Continued from page 53)

optometrists may have 20. But, according to Dr. Lane, ophthalmologists see many more patients than these numbers show.

"How do some doctors see so many patients? They have excellent systems and processes, well-trained staff, efficient office space to do similar type of exams, and the overall physician pace is quick," Dr. Lane said.

Delegation to physician extenders can make the difference in seeing more patients and finding more career fulfillment, he said.

"With a physician-only delegation, the theoretical number of exams that can be done in a day is 19," Dr. Lane said. "As you add the number of physician extenders to carry on various functions of portions of exam—where you have optometrists, physicians extenders, technicians—you can certainly see the amount of time taken to see these patients decreases with extenders and significantly increases number of patients you can see.

"The number of patients obviously increases with an ophthalmologist and technician to 20 regular patients and 2 surgical patients. By adding an optometrist, you can increase the number of surgical patients because of referrals that come from the optometrist," Dr. Lane said.

APPLYING THEORY

To make this theory work in practice takes some initiative on the part of the physician.

"If he or she truly delegates some of the tasks, the doctor will have time to examine more patients," Dr. Lane said. "From observation, a doctor can complete more exams if they're using techs and optometrists. Adding such staff can help optimize use of the ophthalmologist's time so that everyone can each practice within their scope. Everyone then feels fulfilled as a result of this because they feel they are doing what they are trained to do.

"Whether their enjoyment of practice is higher with additional staff is an additional consideration," Dr. Lane added.

"At the end of the day you will feel a whole lot better—even after seeing 60 to 70 patients—when you have all these extenders helping you," he concluded. ■

STEPHEN S. LANE, MD

This article was adapted from Dr. Lane's presentation at the 2014 meeting of the American Society of Cataract and Refractive Surgery. Dr. Lane has no disclosures.

Studies: Practice consolidation influences cost of health care

By Alison Ritchie

SMALL, PRIVATE practices are increasingly merging with larger health-care organizations. Two new studies show that less competition and increased hospital ownership of practices may lead to higher health-care costs.

The first study, conducted by researchers at the University of California, looked at the total expenditures of 4.5 million patients in California covered by a commercial health maintenance organization from 2009 to 2012. The costs included professional, hospital, laboratory, pharmaceutical, and ancillary services. It found that the average total expenditures per patient were 10.3% higher for hospital-owned practices and 19.8% higher for health system-owned practices than those at physician-owned practices.

The second study examined the costs of 10 types of office visits in 1,058 counties across the United States. Researchers at Stanford University used the Hirschman Herfindahl Index to determine the level of competition within the counties. They found that in the least-competitive markets, private provider organizations paid 8.3% to 16.1% more for the same service.

The authors of the Stanford study acknowledged the benefits associated with hospitals acquiring practices, including access to more resources and the ability to better coordinate care. Their findings suggest negative consequences for consumers, however.

"An association between competition and prices may have important implications for health policy, as pressures to increase practice size persist or even increase in the future," the authors wrote. "We saw substantial amounts of concentration in the markets we studied, which raises concerns about potentially harmful implications for consumers. Higher health-care spending due to increased prices paid to physicians without accompanying improvements in quality, satisfaction, or outcomes would generate inefficiency in the health-care system."

Both studies were published in the *Journal of the American Medical Association*. ■

OPHTHALMOLOGY TIMES (Print ISSN 0193-032X, Digital ISSN 2150-7333) is published semimonthly except for one issue in August and December (22 issues yearly) by Advanstar Communications Inc., 131 W First Street, Duluth, MN 55802-2065. Subscription rates: $200 for one year in the United States & Possessions, Canada and Mexico; all other countries $263 for one year. Pricing includes air-expedited service. Single copies (prepaid only): $13 in the United States & Possessions, Canada and Mexico; $20 all other countries. Back issues, if available are $25 in the U.S. $ Possessions; $30 in Canada and Mexico; $35 in all other countries. Include $6.50 per order plus $2 per additional copy for U.S. postage and handling. If shipping outside the U.S., include an additional $10 per order plus $5 per additional copy. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to OPHTHALMOLOGY TIMES, P.O. Box 6009, Duluth, MN 55806-6009. Canadian G.S.T. number: R-124213133RT001, Publications Mail Agreement Number 40612608. Return undeliverable Canadian addresses to: IMEX Global Solutions, PO Box 25542 London, ON N6C 6B2 CANADA. Printed in the U.S.A.

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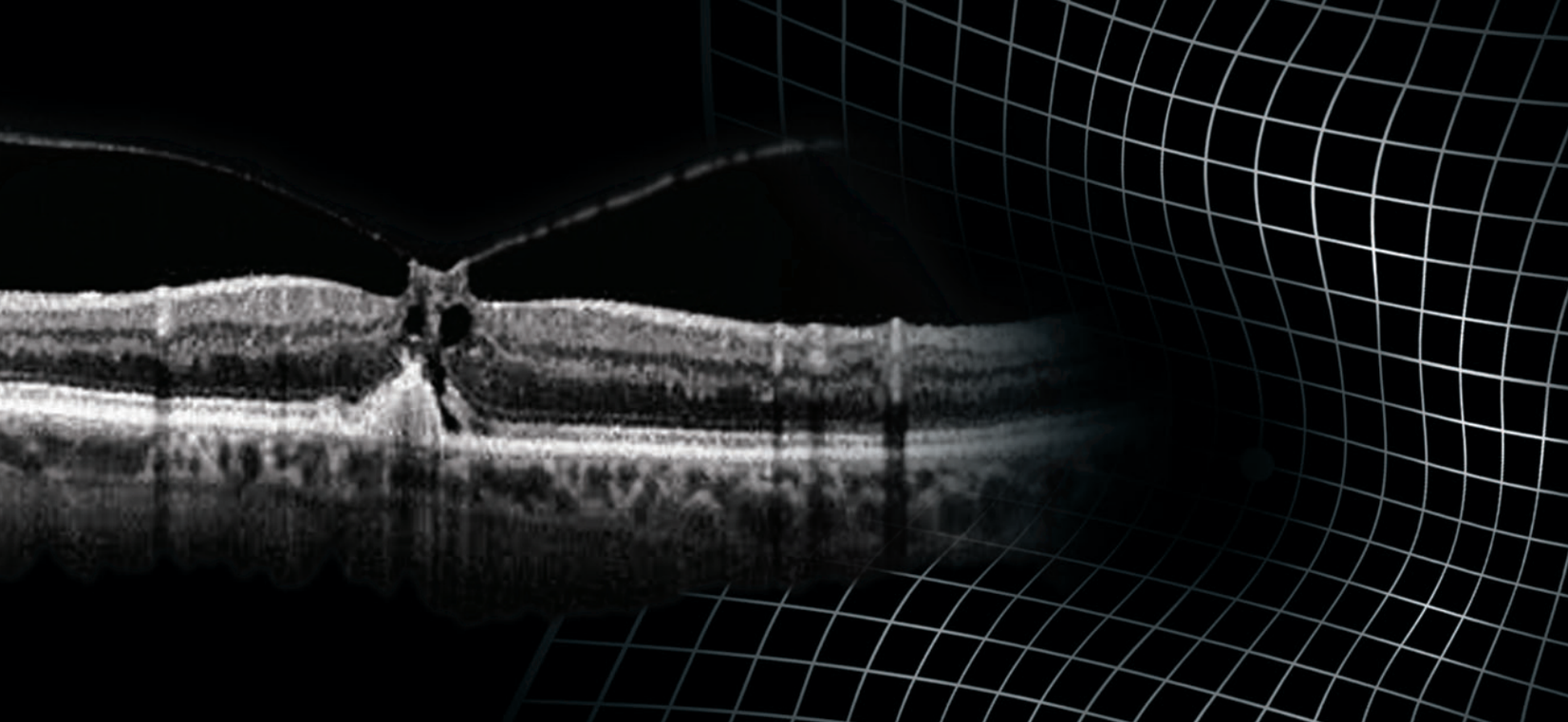

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