GLAUCOMA SPECIALISTS need to think outside the globe because there are multiple considerations pertaining to the orbit and adnexa in patients with glaucoma, said Sunita Radhakrishnan, MD.

"Pathology of the orbit can be a cause of elevated IOP, and the anatomical configuration of the orbit and adnexa may have implications for planning glaucoma surgery," said Dr. Radhakrishnan, private practice, Glaucoma Center of San Francisco, San Francisco. "On the other hand, glaucoma treatments, including medications and surgery, can cause periorbital and adnexal changes."

Some orbital pathologies that can cause an increase in IOP include thyroid eye disease (TED), arteriovenous fistulas, and superior vena cava obstruction. Increased episcleral venous pressure is the underlying mechanism.

Dr. Radhakrishnan noted that TED is the most common orbital cause for increased IOP, but a dural carotid-cavernous fistula which is a low flow arteriovenous fistula, is the diagnosis that is most likely to be missed.

"A dural carotid-cavernous fistula usually presents with prominent episcleral vessels and elevated IOP, but the diagnosis may be missed because it is associated with minimal proptosis," she said. "Establishing the diagnosis is important because dural... (Continues on page 28: Collide)"
When glaucoma and orbit collide

Anatomy, pathology can affect IOP and measurement as well as planning of glaucoma surgery cases

By Cheryl Guttman Krader; Reviewed by Sunita Radhakrishnan, MD

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ADVERSE EVENTS: In 3.3% of patients, reported adverse events of cataract surgery with the 1-Piece IOL included macular edema. Other reported reactions occurring in less than 1% of patients were secondary surgical intervention (pars plana vitrectomy with membrane peel) and lens exchange (due to torn lens haptic).

†Compared against AcrySof® IQ (SN60WF), HOYA AF-1™ FY-60AD and enVista® IOLs (MX60).

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16 ROLE OF SUBTHRESHOLD LASER IN RETINAL DISEASE
Combination therapy benefits from laser in mix for DME, other conditions.

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Uveitis-glaucoma-hyphema syndrome is rare, but seen in a variety of IOLs, explains J. Michael Jumper, MD.

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Study shows limited publications, dearth of information about side effects.

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

1 Can we eliminate the risk of ectasia?

2 OCTA may be harbinger of anti-VEGF efficacy
http://bit.ly/2C60Wfa

3 Understanding achromatopsia
http://bit.ly/2CzC3ve

4 Risuteganib for the treatment of DME

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NOVEL WAY TO TREAT CONJUNCTIVOCHALASIS

To the Editor:

Conjunctival chalasis (conjunctivochalasis) seems to mean different things to different people (See related article, *Ophthalmology Times*, August 2018 issue, Page 11).

I apply this term to a condition where there is an excess of conjunctiva. The conjunctiva may vary from a slight elevation with wrinkling to a cystic elevation the size of a grape. The conjunctival elevation may be caused by an irritation from dry eye, a spastic entropion, etc. Fluid is secreted into the subconjunctival area, which elevates the conjunctiva. Patients may want elevated conjunctiva released due to discomfort or for cosmetic reasons.

I suggest an easy way to release both the elevated conjunctiva and the subconjunctival fluid.

May I call it the “EARL” or EAsy ReLease procedure?

One simply places the warm tip of a hand-held, disposable cautery on the surface of the conjunctival chalasis. The warm tip will produce a hole in the conjunctiva. The fluid under the conjunctiva will run out through the hole, and the chalasis will collapse. The heat produces a coagulum around the conjunctival hole that sticks the conjunctiva to the subconjunctival tissues. One hole is all that is needed.

I explain the procedure to the patient and provide him with an antibiotic drop to use for a few days prior to the procedure. One needs to place a topical anesthetic in the eye and then insert a strong eye speculum. Turn the cautery on and then turn it off and wait a few seconds so the tip will be warm but not very hot. If the tip is too hot the patient will feel the heat and jump.

I have not had to repeat the procedure but I’m sure that one may repeat it if necessary. I understand some surgeons excise conjunctiva and may place an amniotic membrane graft. I have not found this necessary.

—Earl Braunlin, MD
Fort Wayne, IN

Letters to the Editor may be submitted to sheryl.stevenson@ubm.com. Letters may be edited for clarity and length.
INDICATION FOR USE.
The iStent inject® Trabecular Micro-Bypass System Model G2-M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma.

CONTRAINDICATIONS.
The iStent inject is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure.

WARNINGS.
Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard.

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The iStent inject is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details.

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The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent inject have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with...prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents.

ADVERSE EVENTS.
Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent inject vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss > 2 lines > 3 months (2.6% vs. 4.2%).

CAUTION: Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.


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Do machines think?
Whether we like it or not, artificial intelligence has arrived

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.

“I think, therefore I am.” —Rene Descartes

AS YOU KNOW, artificial Intelligence (AI) has been getting a lot of attention these days in the lay press, in our science journals, and in movies. Recently, the FDA granted its approval to an AI/machine learning approach to the analysis of retinal photographs to screen for diabetic retinopathy based upon data suggesting that the approved AI approach may actually be superior at detecting retinal disease than relying on a human diagnostician.

From recent conversations, I learned that AI commonly evinces strong feelings, positive and negative:

- A medical school dean told me that he thinks AI will streamline the diagnosis of most medical illnesses. He believes this will make the career path of primary care physician much less interesting in the future, and he is encouraging his own child to consider becoming an ophthalmologist.
- IBM thinks its Watson computer will improve the outcomes of cancer therapy, improving patient care while generating a revenue stream for the company.
- A physician friend worries, like the famous physicist Stephen Hawking, that AI will be an existential threat to the human race. This vision of a dark future includes autonomous lethal devices taking human life.
- Another physician friend sees AI as a friend and servant of humans. Autonomous vehicles, for example, will make travel ever safer, eventually dramatically reducing traffic fatalities.

All this attention has caused me to look into the field of philosophy of artificial intelligence and what it means to think. In 1950 mathematician Alan Turing wrote a paper entitled “Computing Machinery and Intelligence” that began: “I propose to consider the question, ‘Can machines think?’”

Turing conceived the test that today bears his name. The Turing test says that a machine will have exhibited intelligence equivalent to a human when a human, sitting at a keyboard and typing back and forth with an unseen correspondent, cannot tell after several minutes whether the responses are those of a machine or another human. So far, no wonder of computing technology has yet passed this test.

One AI test involved a machine analyzing performances of famous comedians. After, the machine was tasked with writing its own jokes. The results are laughable. While curious and perhaps interesting, these computer-authored jokes are more devoid of humor than the least funny human-authored jokes you have ever heard.

Most of my friends believe that computers today can think to some degree, and in the future with certainty will be able to mimic human thought and conversation.

“If they can think,” I asked, “does that also mean they are alive?” Isn’t that what Descartes had in mind with his famous quote?

My friends would not make this leap. The consensus was thought and life are not synonymous. For example, a machine might be capable of thought but not be alive in the same way that a single-celled organism, like Staphylococcus, might be alive but not capable of thought.

Machines are demonstrating more capability to perform tasks like interpreting x-rays or detecting diabetic retinopathy without human oversight. Wise physicians in the future will harness that technology, freeing them up to do what highly-trained humans can do best (like stand-up comedy and injecting bevacizumab).

My own view is that AI will be an overall force for good, but there is no reason why it will not be misused by some for criminal or malevolent ends.

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XIIDRA MAY INTERRUPT THE CYCLE OF INFLAMMATION CENTRAL TO DRY EYE DISEASE¹,²

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Xiidra blocks the interaction of ICAM-1 and LFA-1, which is a key mediator of the inflammation central to Dry Eye Disease. In vitro studies have shown that Xiidra may inhibit the recruitment of previously activated T cells, the activation of newly recruited T cells, and the release of pro-inflammatory cytokines.³

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration. Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Check out Xiidra-ECP.com
BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

 Dosage and Administration
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. Mutagenesis: Lifitegrast was not mutagenic in the in vitro Ames assay. Lifitegrast was not clastogenic in the in vivo mouse micronucleus assay. In an in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD]) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.
Joint event to feature plenty of symposia, practice management programs, product innovations

By Beth Thomas Hertz

Mix art and science together and what do you get? The theme for the 2018 meeting of the American Academy of Ophthalmology (AAO), which is being held in conjunction with the Pan-American Association of Ophthalmology (PAAO). The combined event convenes Saturday, Oct. 27 through Tuesday, Oct. 30 in Chicago, and is officially themed “Art + Science.”

The theme was chosen because it connects to both Chicago and ophthalmology, said Maria M. Aaron, MD, secretary for the annual meeting.

Chicago has a long history of art, showcasing the Bean sculpture and the Art Institute of Chicago, as well as science, featuring the Field Museum and the Museum of Science and Industry, she noted.

“And while ophthalmology is obviously a science, it’s the art that differentiates the virtuosos from the average; it’s what most ophthalmologists aspire to,” she said. “Our role as ophthalmologists is to practice the art of genuinely caring for the whole person and communicating compassionately. That’s what makes being a doctor a privilege.”

Dr. Aaron said the academy also plans to offer some art-related sessions at the annual meeting, including the Michael F. Marmor Lecture in Ophthalmology and the Arts, which will be Monday from 12:45 to 1:45 p.m. In it, Howard Schatz, MD, will speak on the topic “In Search of Wonder.”

NEW THIS YEAR

Dr. Aaron highlighted what’s new this year. There will be more of the increased Saturday programming including the International Council of Ophthalmology conference for ophthalmic educators, coding sessions, American Academy of Ophthalmic Executives (AAOE) practice management...
master classes, and two Academy Café sessions on neuro-ophthalmology and cataract, according to Dr. Aaron.

“We’re offering eight symposia on topics, such as vision rehabilitation, neuro-ophthalmology, and globalizing human resources; plus the highly interactive, competitive Diagnose This Live. And we’re offering more Skills Transfer labs on Saturday,” Dr. Aaron said.

Also new this year, will be the AAOE Practice Management Program on Friday, with two sessions: (Re)Focus on Remarkable Patient Care Experiences and Top Strategies for Successfully Running Your Retina Practice.

“These sessions are recommended for physicians as well as practice managers,” she said.

HOT TOPICS
Dr. Aaron listed three spotlight sessions on hot topics this year:

1. Spotlight on Common Approaches to Ophthalmic Urgencies: Sunday, 10:15–11:45 a.m.
2. Spotlight on Cataract Complications: Pressure Cooker — Managing Nerve-racking Complications, featuring the Charles D. Kelman Lecture: Monday, 8:15 a.m.–12:15 p.m.
3. Spotlight on the Art of Patient Communication: How to Handle the Unhappy Patient: Monday, 2–3:30 p.m.

Of 55 planned symposia, she said the academy predicts these to be especially popular:

1. Medical Scribes in the EHR Era: Monday, 12:15–1:45 p.m.
2. Is This Optic Nerve Normal? Monday, 8:30–10 a.m.

FOLLOWING ARE OTHER PLANNED MEETING HIGHLIGHTS:

OPENING SESSION
The opening session, starting at 8:30 a.m. Sunday, will feature the Jackson Memorial Lecture, given this year by Philip J. Rosenfeld, MD, PhD, director and professor of ophthalmology at the Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine. His topic will be “Lessons Learned from Avastin and OCT: The Great, The Good, The Bad, and The Ugly.”

The Laureate Award will be given to Steven T. Charles, MD, clinical professor of ophthalmology at the University of Tennessee, who has developed many of the techniques and devices used by vitreoretinal surgeons worldwide.

OTHER AWARDS TO BE GIVEN AT THE OPENING SESSION:

1. DISTINGUISHED SERVICE AWARD: Directors of Medical Student Education in Ophthalmology. Rukhsana Mirza, MD, will be accepting.
2. SPECIAL RECOGNITION AWARD: Ophthalmology Section of the National Medical Association. Chasidy D. Singleton, MD, will be accepting.
3. OUTSTANDING HUMANITARIAN SERVICE AWARD: David Heiden, MD, and William L. White, MD
4. OUTSTANDING ADVOCATE AWARD: Bradley C. Black, MD
5. INTERNATIONAL BLINDNESS PREVENTION AWARD: Jacob Pe’er, MD
6. STRAATSMA AWARD FOR EXCELLENCE IN RESIDENT EDUCATION: Preston Blomquist, MD
7. VISIONARY SOCIETY AWARD: Ophthalmic Mutual Insurance Company (OMIC)
8. GUESTS OF HONOR: Wallace L. M. Alward, MD, Paul R. Lichter, MD, and Jeffrey A. Nerad, MD

AAO booth #545
Buy Early • Save Money Limited Inventory
Continues on page 14: AAO lineup
What wavefront data do you use to select EDOF IOLs for patients?

The OPD-Scan III lets me know if I have to correct any astigmatism. Angle alpha and angle kappa let me know I’m in that zone where it’s safe to use EDOF lenses. And the placido disk mires show me if the ocular surface is healthy – or identify the patients with poor ocular surfaces that will not have great outcomes.

There are fewer halo and glare issues with EDOF lenses than their predecessor, multi-focal IOLs. However, I still look at the higher order aberration map on my OPD-Scan III because if that cornea is not healthy, if it has a lot of higher order aberrations, they may not be a good candidate for the EDOF lens. I use these maps to reinforce the points I am discussing.

When we’re looking at the true multi-focal lenses, the stronger their ADD, the tighter your tolerance has to be for angle alpha and angle kappa and as you get lower power, you get a little bit more leeway with the EDOF lenses. The OPD is essential for this data... we depend on it and we’ve really been impressed by it.

There are cases that I miss the opportunity to avoid. That’s the case with any multi-focal or extended depth of focus lens; there will be patients who will not necessarily be the best candidate and you’re not always going to be able to predict that ahead of time. This advanced OPD can lessen the number of patients who may be disappointed.

Though the EDOF is a more forgiving technology, remember that it’s reverse engineering the cornea. It’s more forgiving if you have regular astigmatism or if you have a little bit of macular pathology, but if you have any type of corneal edema, these are the patients who are going to surprise you. By simply observing the OPD placido rings, you can really stay out of trouble.
PAAO LINEUP

(Continued from page 12)

EYE PLAY EXPERIENCE
EyePlay Experience was a new feature last year, Dr. Aaron said. “It was so fun, we’re doing it again this year,” she said.

Located in South Hall A, Booth 2581, this is a place to go to relax, energize, and stimulate your mind. There will be therapy dogs as well as bunnies and bunny goats.

There will also be seated massages, games, and a beer garden serving ale made with hops grown at McCormick Place. Attendees can also assemble hygiene bags for those in need and take a selfie with a giant rabbit.

ORBITAL GALA
The Orbital Gala from 6 to 10 p.m. Sunday is a fun time to catch up with friends while helping a good cause. This year’s theme is the 1960s. Wear psychedelic prints while enjoying what the academy promises to be groovy entertainment, far-out food, and a silent auction at this 15th annual event that raises money for the new Museum of Vision.

The gala will be held at the Chicago Cultural Center. Business or cocktail attire is appropriate. Tickets are $300 for ophthalmologists and their guests, with a discounted ticket of $150 available for young ophthalmologists.

NAMED LECTURES
Many of these lectures are held as part of a larger session. Here’s the lineup:

SUNDAY, 10:15–11:45 A.M.
■ Whitney G. Sampson Lecture, “Simple Limbal Epithelial Transplantation,” Kathryn A. Colby, MD, PhD
■ Ruedemann Lecture, “Choosing the Ideal Implant Size, an Oculist’s Perspective,” Joseph A. LeGrand, Jr., BCO
■ Barraquer Lecture, “Lenticular Implantation and Refractive Eye Banking as a New Frontier in Refractive Surgery,” Ronald R. Krueger, MD

SUNDAY, 12:45–1:45 P.M.
■ G. Stephen and Frances Foster Lecture on Uveitis and Immunology, “The Eye Fights Back: Immune Defense in a Dangerous World,” given by Janet L. Davis, MD

SUNDAY, 2–3:30 P.M.
■ Robert N. Shaffer Lecture, “At the Technological Confluence of Glaucoma Clinical Care and Research,” Sayoko E. Moroi, MD, PhD

SUNDAY, 3:45–5:15 P.M.

MONDAY, 8:15 A.M.–12:15 P.M.
■ Charles D. Kelman Lecture, “Dealing with Damaged Zonules,” Robert J. Cionni, MD
■ Jones/Smolin Lecture, “The Persistent Enigma of Adenovirus Keratitis: Viral Pathogenesis in the Cornea,” James Chodosh, MD, MPH

MONDAY, 8:30–10 A.M.
■ William F. Hoyt Lecture, “Unraveling the Enigma of Non-Arteritic Anterior Ischemic Optic Neuropathy,” Joseph F. Rizzo III, MD

MONDAY, 2–3:30 P.M.
■ Zimmerman Lecture, “Retinoblastoma: Seeing the Big Picture,” Matthew W. Wilson, MD

MONDAY, 3:45–4:45 P.M.
■ Dr. Allan Jensen & Claire Jensen Lecture in Professionalism and Ethics, “The Intersection of Liability and Ethical Professionalism,” Anne M. Menke, RN, PhD

TUESDAY, 8:30–10 A.M.
■ Marshall M. Parks Lecture, “Evidence-Based Amblyopia Treatment,” Jonathan M. Holmes, MD
■ Arnall Patz Lecture, “Is All Cystoid Macular Edema the Same?” Alexander J. Brucker, MD

TUESDAY, 10:15 A.M.–12:15 P.M.
■ Castroviejo Lecture, “The Ethical Basis of Clinical Research,” Alan Sugar, MD

PAN-AMERICAN ASSOCIATION OF OPHTHALMOLOGY
The following sessions will be held jointly with the AAO and PAAO:

■ Symposium: Simplifying Open Angle Glaucoma Management...What Matters, Sunday, 10:15–11:45 a.m.
■ Symposium: Surgical Innovations in Retina Across the Americas, Monday, 8:30–10 a.m.
■ Symposium: Corneal Infections and Kerato-planty: Perspectives From the AAO and PAAO, Tuesday, 8:30–10 a.m.

Also, the 32nd Best of the Academy in Spanish 2018 will be held Wednesday from 8 a.m. to 5:30 p.m. This event will summarize the important presentations in general ophthalmology and all subspecialty fields from the AAO annual meeting. New ophthalmic literature and instruments also will be objectively evaluated. The presenting panels will be composed of Spanish-speaking ophthalmologists. Advance registration is requested.

EXHIBIT HALL
Check out the large exhibition of ophthalmic technology, products and services in the exhibit hall.

It will be open Saturday through Monday from 9 a.m. to 5 p.m. and Tuesday from 9 a.m. to 1 p.m.

SUBSPECIALTY DAY
Eight Subspecialty Day meetings will take place before the main meeting begins. Separate registration is required. Details are at https://www.aao.org/annual-meeting/subspecialty-day.

FRIDAY ONLY:
■ Refractive Surgery Subspecialty Day 2018: Better Together — Lens- and Cornea-Based Surgery

FRIDAY AND SATURDAY:
■ Retina Subspecialty Day 2018: The Art + Science of Retina + Vitreous
■ Glaucoma Subspecialty Day 2018: What’s Tried, True, and New
■ Ocular Oncology and Pathology Subspecialty Day 2018: Hot Topics in Ocular Pathology and Oncology — An Update
■ Oculofacial Plastic Surgery Subspecialty Day 2018: Oculoplastics Real World: Real Cases, Real Lessons, True Learning
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LASER’S POSITION in surgeons’ treatment armamentarium for diabetic eye disease has changed: once it was in the forefront; now, in the setting of injections—both anti-VEGF and steroids—laser is playing second or third fiddle. Its utility in a patient’s overall treatment strategy, however, is still important.

Subthreshold laser, referring to any subvisible laser photocoagulation, in general is underutilized as a treatment modality in retinal vascular conditions from diabetic macular edema to proliferative diabetic retinopathy to retinal vascular occlusion and central serous retinopathy.

Prior to the use of subthreshold technology, conventional continuous wave laser panretinal photocoagulation or PRP was used to reduce ischemic effects. PRP, however, led to retinal atrophy and thinning, sometimes creating scotomas and causing other complications. Investigators soon learned how to apply the therapeutic effect of lasers while minimizing the damage. At the same time, they realized that it was not necessary to create full-thickness retinal damage to obtain a therapeutic benefit. Conventional PRP laser uses longer-duration continuous wave therapy, delivering the same magnitude of energy during the entire treatment and causing significant collateral damage. Subthreshold laser, on the other hand, results in similar therapeutic benefits with no visible damage.

SUBTHRESHOLD LASER TREATMENT

The laser’s hyperthermal energy stresses the retinal pigment epithelium in such a way as to cause a cellular cascade that produces a therapeutic benefit. Subthreshold therapy seeks to maintain the temperature below the threshold of irreversible thermal damage. Several techniques have evolved to apply energy in this manner.

MICROPULSE

Iridex introduced subthreshold MicroPulse Diode laser photocoagulation in the 1990s using an 810-nm laser. The energy is delivered in microsecond-long bursts of short, repetitive pulses, with periods of cooling in between. This technique allows effective subthreshold tissue-sparing laser treatments without visible burns to the RPE, and the surgeon can vary the power as necessary depending on the desired endpoint. The lack of chorioretinal scarring allows the surgeon to apply treatments close together, and treatments can be repeated without causing noticeable retinal scarring.

EPM

The PASCAL pattern scanning laser (Topcon) uses pattern scanning with a shorter pulse duration of 10 to 30 milliseconds. At the correct power, temperature rises induce changes in various proteins leading to cellular damage, but not death. The EndPoint Management (EpM) system uses a computational model of retinal heating and the Arrhenius integral to determine optimal laser parameters. The EpM strategy begins retinal treatment with the titration of the laser power to a minimally visible threshold burn as a baseline. The treatment is defined as a percentage of this level, and then EpM adjusts laser power and pulse duration to this level. Many spots can be quickly placed.

MY EXPERIENCE

After originally using implementing Iridex subthreshold laser; my practice has used the Topcon laser with EpM for the past 2 years. Routinely, we incorporate subthreshold laser for patients with diabetic macular edema as well...
as other retinal vascular conditions like retinal vein occlusion and central serous retinopathy.

My overall goal is to expedite a patient’s visual recovery and anatomical normalization as soon as possible.

In a subset of patients, this is sometimes best achieved with combination therapy. I find that subthreshold laser with EpM is effective following anti-VEGF therapy in patients who have a dry retina to help keep it dry and reduce the need for additional long-term injection therapy. Subthreshold laser is useful as adjunctive treatment in more challenging or recalcitrant eyes that have reached their response threshold with anti-VEGF and/or steroid shots.

**TITRATE POWER**
With EpM, as compared with MicroPulse, the surgeon can visually titrate the amount of power that is needed for an individual eye, in real time. This means I can identify the minimum amount of power that I need to deliver to achieve a therapeutic effect. Other platforms without EpM require the surgeon spend time making additional and perhaps unnecessary spots, trying to achieve the correct power. Another benefit of EpM is the ability to apply anchoring burns to mark previous treatment.

At around the 8- or 12-week follow-up, I can typically see a therapeutic effect. In terms of endpoints, I am looking for, anatomically, the fluid resolving and a dry state post anti-VEGF. I also expect to see a visual improvement, as the presumption is that fluid accumulation participates in patients’ visual decline.

**OUTCOMES, ROLE**
Vision is more than one’s ability to read an eye chart. Contrast sensitivity is important to patients although it is not something we measure in the office. It is, however, a component of patients’ perception of a visual improvement.

Certainly, patients are not lining up to have invasive procedures, and they all want visual recovery in the quickest and least complicated way possible.

Although injections remain a primary therapy for retinal vascular conditions, and some may have only a handful of injections and be virtually cured, sicker patients will require multimodal treatments.

Subthreshold laser provides seamless adjunctive therapy that can supplement or obviate the need for future injections in certain retinal conditions.

We only have a handful of go-to treatments, so it is nice to have an alternative to injections that does not result in visual damage.

The Topcon laser is not FDA approved for central serous retinopathy.

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**References**


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**NETAN CHOUHRY, MD,** is the cofounder and medical director of the Vitreous Retina Macula Specialists of Toronto. He may be reached at Netan.choudhry@vrmto.com. Dr. Choudhry is a consultant to Topcon.

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Clinical teaching across the Atlantic: Learning in action
What U.S., European surgeons teach each other about MIGS, glaucoma interventions

By Davinder S. Grover, MD, MPH, and Ingeborg Stalmans, MD, PhD; Special to Ophthalmology Times

A CONTINUOUS, HEALTHY exchange of clinical information and new ideas takes place between glaucoma surgeons in the United States and Europe every day. We enjoy learning from each other, particularly as surgeons on one continent earn experience with a new device or technique and their peers on the other side of the Atlantic want to know more about it. We are also continuously curious about the way our peers work, such as the flexibility or freedom they are permitted in devising the best treatment for each patient. Many factors influence how and why glaucoma surgery varies in our different parts of the world, but our commitment to sharing our experiences remains constant.

A “HEAD START” ON GLAUCOMA DEVICES AND TECHNIQUES

One reason so much teaching takes place across the miles is the disparity in access to glaucoma devices and techniques. Differences in the approval process for FDA and CE Mark approval tend to make devices available in the EU before the US. The FDA requires proof of both safety and efficacy, whereas for CE Mark approval, researchers can supply safety data alone and track efficacy once the device is in the hands of practicing physicians.

Today, for example, European surgeons using the InnFocus MicroShunt (InnFocus) are drawing the interest of surgeons in the US, where FDA trials are now underway. The Hydrus microstent (Ivantis), which was FDA approved in August, also has been available in Europe for some time.

A few years ago, the XEN Gel Stent (Allergan) offered learning opportunities on both continents. XEN was available in Europe several years before US surgeons had access to it, so US surgeons were able to learn from their peers’ experiences. At the same time, the FDA clinical trial required use of mitomycin C on a sponge under the conjunctiva, which differed from the European approach of subconjunctival injection. Both methods were effective, and now surgeons on the US feel comfortable using either approach because the data support both.

While surgeons in the EU tend to have earlier access to devices used to treat glaucoma, American glaucoma surgeons may have more experienced with new techniques. One reason is that certain MIGS techniques have been developed in the US. For example, Malik Y. Kahook at the University of Colorado invented the Kahook Dual Blade (New World Medical) instrument and technique for goniotomy. European surgeons have little or no experience with this MIGS procedure and are learning about it through their American peers. Gonioscopy-assisted transluminal trabeculotomy (GATT) is not used very much in Europe, either, so Americans with significant experience doing GATT are teaching EU surgeons.

FREEDOM AND FLEXIBILITY

In addition to access to new procedures, EU and US surgeons can differ in terms of the amount of freedom and flexibility they have to use those procedures and to explore new avenues. European surgeons have the flexibility to use multiple MIGS implants such as Hydrus and iStent, for instance, as well as to use those devices outside of cataract surgery. These approaches would not be reimbursed for surgeons in the US, but their European peers are more likely to be approved based on the balance of outcomes and costs.

The flexibility to use many MIGS devices as standalone procedures not only leads to different indications, but also reflects the trend in Europe for glaucoma surgeons to perform most glaucoma procedures, rather than turn them over to cataract surgeons. That trend, which generally results in more solo procedures than cataract-MIGS combinations, allows European surgeons to intervene in cases of advanced or aggressive glaucoma without waiting until the patient’s cataracts warrant surgery.

US surgeons tend to be more flexible than their European peers in performing manipulations related to glaucoma procedures such as bleb work and needling at the slit lamp, rather than in the OR. This difference may be related to the costs of OR time in the US, compared to some European countries.

LEARNING EXPERIENCES

In addition to following the literature, many surgeons take advantage of online videos of our peers’ talks and surgeries. Videos are welcome opportunities to get specific information in a very convenient format.

It is especially helpful to listen to peers with access to many surgical techniques and devices for glaucoma, so we can understand not only how they are used, but also how they are selected and/or combined. Because we do not have side-by-side comparisons of most glaucoma treatment modalities, and study designs vary for MIGS and other procedures, experienced surgeons’ perspectives on how they weigh treatment choices for their patients are particularly valuable.

Perhaps the richest source of learning is a face-to-face meeting at international conferences. For surgery in particular, small groups and workshop offer the important opportunity to ask questions about specific cases. Skype lectures are productive as well, but small workshops are most enjoyable for us as both attendees and lecturers for sharing experiences with peers, from close to home and far away.

TAKING HOME

Surgeons enjoy learning from each other, particularly as surgeons on one continent earn experience with a new device or technique and their peers on the other side of the Atlantic want to know more about it.

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Despite advances in diabetic eye disease, questions persist
Factoring in that patients require continual and constant monitoring, maintenance

By Michelle Dalton, ELS; Reviewed by Rishi P. Singh, MD

WITH ALL the technological and medical advances for the treatment of diabetic eye diseases, “we still have this ongoing therapy issue because, unfortunately, our patients require continual and constant monitoring and maintenance,” said Rishi P. Singh, MD, of the Cole Eye Institute, speaking here during the American Society of Retina Specialists annual meeting. Dr. Singh is this year’s ASRS President’s Retina Young Investigators Award recipient.

Dr. Singh concentrated on the outstanding questions in diabetic eye disease. For instance, what can imaging tell clinicians about the cause of vascular diseases, in particular, diabetic retinopathy (DR)?

“What can imaging tell us about the cause of diabetic eye disease? What drives ischemia in diabetic eyes? Is it solely retinal capillary closure?”

**LESSONS LEARNED FROM IMAGING**
Clinicians often think of diabetic eye disease as limited to the retina, but Dr. Singh and colleagues have found that is not necessarily the case.

In one study on choroidopathy using optical coherence tomography (OCT) angiography, eyes with nonproliferative DR and proliferative DR (PDR) showed significantly decreased choriocapillaris whole image and parafoveal CPD compared to controls. Only eyes with PDR showed significantly decreased retinal whole image, foveal, and parafoveal CPD. Only eyes with PDR showed significantly increased FAZ values. (Figures courtesy of Rishi P. Singh, MD)

**TAKE-HOME**

▶ In his ASRS President’s Award Lecture, Rishi P. Singh, MD, addresses advancing insights into diabetic eye disease, including imaging modalities and intravitreous treatment.

“Proliferative patients manifest decreased in CPD, especially in the parafoveal region,” he said. “It’s important to think about the patient as a whole, and realize that diabetes is a retinal disorder, but may also be a choroidal disorder as well. The vessels below the retina may also contribute to the ischemia and changes that we see in diabetic eye disease.”

The DCCT Research Group found patients on “really intensive medical therapy actually worsen for a short period of time, usually the first 2 years,” Dr. Singh said. “Their DR gets worse as a result of being under really tight control and this has been found in numerous clinical trials since.”

Continues on page 22: Diabetic
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More patients treated with nepafenac experienced a 15 letter improvement from baseline more patients treated with nepafenac experienced a 15 letter improvement from baseline. BCVA improvement of ≥15 letters from preoperative baseline to Day 14 and maintained through Day 90.

(FIGURE 3) More patients treated with nepafenac experienced a 15 letter improvement from baseline more patients treated with nepafenac experienced a 15 letter improvement from baseline. BCVA improvement of ≥15 letters from preoperative baseline to Day 14 and maintained through Day 90.

(FIGURE 4) Treatment with nepafenac resulted in improved ME rates over placebo. In both studies, a significantly lower proportion of patients in the nepafenac versus the vehicle group developed ME within 90 days following anti-VEGF therapy for diabetic macular edema. The results of pooled analysis confirmed the finding of these individual studies.

(Continued from page 20)

In the STAMPEDE study, researchers looked at patients who underwent bariatric surgery and found a “dramatic and rapid reduction in A1C mostly in the first 6 months with a net reduction of nearly 3% at 12 months with persistent effects of 2.5% at 36 months,” he said. At both 2 and 5 years, there was no significant difference in retinopathy scores or step progression within treatment groups from baseline across cohorts. “That’s very different from what the DCCT group found.”


RISHI P. SINGH, MD, is a consultant for Allergan, Genentech, Optos, Regeneron, Shire, and Novartis. He conducts sponsored research for Akebia, Novartis, Apellis, Genentech/Roche, and Regeneron.

References
Considering use of teprotumumab in thyroid eye disease patients

There is need for alternative treatment to circumvent current treatment limitations

Neuro Connection By Alexis Pascoe, Iyza F. Baig, and Andrew G. Lee, MD

GRAVES’ DISEASE is an autoimmune disease characterized by an autoantibody-stimulated thyroid gland leading to enlargement and hyperthyroidism. Features include increased heart rate, increased metabolic rate, and ocular abnormalities such as proptosis. Graves-mediated ophthalmopathy is also known as Thyroid Eye Disease (TED). Glucocorticoids and radiotherapy are the current mainstay of treatment for TED but are associated with inconsistent results and a variety of side effects such as urinary tract infections, glucose intolerance, Cushingoid features, and hot flashes. In addition, proposis resolution is minimal when treating with glucocorticoids and radiotherapy. If TED reaches the extent of compressive optic neuropathy, corneal exposure, or orbital congestion, decompression surgery is indicated, but evidence of its effectiveness is limited. In addition, a common postoperative complication is debilitating strabismus. A possible therapeutic agent was rituximab, but trials have shown conflicting evidence regarding its effectiveness. Therefore, there is a need for an alternative treatment that can circumvent the current treatment limitations.

The pathogenesis of Graves’ disease has been linked to the presence of TSHR antibodies. TSHRs are found in orbital tissues and orbital fibroblasts, and their stimulation has been linked to the accumulation of hyaluronan and the expansion of connective and fat tissue that leads to TED. However, according to numerous in vitro studies, IGF-IR is also overexpressed in Graves’ disease, and autoantibodies recognizing and activating the IGF1R protein occurs in the condition as well. Furthermore, Tsui et al. compared the levels of TSHR versus IGF1R protein expression in orbital fibroblasts of TED patients, and found that levels of IGF1R were much higher than TSHR levels, which were scantily expressed. Evidence suggests that the activity of thyrotropin and thyroid stimulating antibodies depend on the activity of IGF-1R to some degree. Furthermore, through IGF-IR activation, fibroblasts have been shown to produce chemoattractants that cause infiltration of the orbital tissue by T cells and B cells. IGF-IR and TSHR also form a receptor complex that when activated causes the activation of both receptors. Because IGF-IR antibodies have been shown to mitigate the TSHR antibodies, blocking the stimulation of IGF-IR disrupts the pathway for the orbital tissues expansion of TED. Therefore, due to its potential role in the pathogenesis of TED, treatment with a human IGF-IR monoclonal antibody, teprotumumab, was proposed. In 2017, the results of a recent double blinded, randomized controlled trial of teprotumumab showed great promise in alleviating proptosis, diplopia in improving the quality of life of patients with TED.

To evaluate the efficacy of teprotumumab, a double-masked, randomized, multicenter, placebo-controlled trial was performed by Smith et al with three phases:
1. A screening phase, lasting 2–6 weeks
2. An intervention phase, lasting 24 weeks
3. A follow-up phase, lasting 48 weeks

Efficacy of treatment was measured by Clinical Activity Scores, Hertel exophthalmometer measurements, Graves’ ophthalmopathy-specific quality-of-life (GO-QO) score, and subjective diplopia assessment.

Results showed that the difference between the trial group and the placebo group was apparent by week 6 with 43% of the teprotumumab group having a response in terms of the assessment factors listed above while only 4% of the placebo group experienced a response with a statistically significant difference between the two. At week 24, 69% of the teprotumumab group and 20% of the placebo group experienced statistically significant reduction in assessment factors. Ultimately, the trial found that treatment with teprotumumab lead to statistically significant and clinically relevant reduction in subjective diplopia, Clinical Activity Score, proptosis, and GO-QOL (3). The main adverse effect noted was hyperglycemia, which did not worsen after teprotumumab treatment.

In conclusion, the double-masked, randomized, multicenter, placebo-controlled trial by Smith et al demonstrated that a 24-week course of teprotumumab benefits patients with moderate to severe Graves ophthalmopathy by enhancing quality of life as well as reducing their Clinical Activity Score and proptosis. Although a similar reduction in proptosis can be achieved with decompression surgery, this drug doesn’t include the risk of recurrence or strabismus exacerbation. The long-term benefits of teprotumumab are still in the process of being explored and future studies are required to establish its efficacy compared to glucocorticoids and assess the safety profile of the drug long term. Based on these results however, teprotumumab shows significant promise in the treatment of TED, and ophthalmologists should be aware of the drug as a viable therapeutic option.

References

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Alzheimer's disease biomarkers in the vitreous: What a study has shown

By Michelle Dalton, ELS; Reviewed by Manju L. Subramanian, MD

ALZHEIMER'S disease leads to severe cognitive dysfunction and eventual death; by 2050 it is expected to affect more than 115 million people worldwide. From time of diagnosis until death the average survival time is just under 5 years. Even with advances in medicine, a clinical diagnosis is only confirmed post-mortem, said Manju L. Subramanian, MD, Boston Medical Center.

Most patients will be asymptomatic until later stage of disease, which can be too late for current therapies to have any meaningful effect, she said.

“There is a need for sensitive and specific tests for the early diagnosis of Alzheimer’s,” she said. “The study confirms that Alzheimer’s disease biomarkers exist in the vitreous, and their correlation to cognition suggest that protein biomarkers in the vitreous has a potential role as an early diagnostic tool.”

STUDY DETAILS

Dr. Subramanian initiated a cross-sectional study to determine if known biomarkers for Alzheimer’s disease in the vitreous humor correlated with cognitive function. She enrolled 80 patients already scheduled for vitrectomy who then underwent a mini-mental status examination (MMSE) to assess cognitive function. A diagnosis of dementia or Alzheimer’s was not exclusionary.

Of those 80 subjects, nine (5 males, 4 females) exhibited mild (n=6) to severe (n=1) levels of cognitive impairment based on MMSE scores.

Vitreous samples were taken (0.5-2.0 mm undiluted), and the samples were analyzed by ELISA. Higher vitreous levels of Aß40 (p = 0.015), Aß 42 (p = 0.0066), and tTau (p = 0.0085) were significantly associated with better MMSE scores, while lower vitreous levels were associated with lower MMSE scores.

“One of the remarkable findings of our study is the correlation between dementia and Alzheimer’s disease in the vitreous humor. Patients with eye disease are probably an at-risk population for Alzheimer’s disease. We see patients with eye complications from diabetes, and Type 2 diabetes is a well-known risk factor for Alzheimer’s,” Dr. Subramanian said. “So whatever we’re able to find in patients with eye disease may be generalizable to the rest of the population as well.”

NEXT STEPS

For Dr. Subramanian, the next step in the research is how to translate the data into something that is clinically useful. There may be a role for optical coherence tomography (OCT) as well, and several studies have shown significant findings in patients with cognitive impairment. But other eye diseases like glaucoma affect the nerve fiber layer in a similar manner as Alzheimer’s, which may limit the effectiveness of OCT, she said.

“Patients with eye disease are probably an at-risk population for Alzheimer’s disease. We see patients with eye complications from diabetes, and Type 2 diabetes is a well-known risk factor for Alzheimer’s,” Dr. Subramanian said. “So whatever we’re able to find in patients with eye disease may be generalizable to the rest of the population as well.”

THYROID

(Continued from page 24)


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carotid-cavernous fistula can often be cured with endovascular intervention.”

Before planning surgery for uncontrolled IOP, the possibility that orbital and lid anatomy is affecting the accuracy of IOP measurement should be considered.

For example, prostaglandin associated periorbitopathy (PAP) that can develop in patients on long-term treatment with a topical prostaglandin analogue can be associated with a horizontally tight upper eyelid that makes applanation challenging and results in artifactually elevated IOP.

“In patients with PAP, it may be difficult to raise the upper eyelid enough so that it clears the top of a Goldmann applanation prism,” Dr. Radhakrishnan said.

Tonometers that have a smaller area of corneal contact (like the Icare rebound tonometer) can be helpful in these patients.

Restricted ocular motility in patients with TED caused by a tight inferior rectus muscle can also lead to artifactually high IOP. Measuring applanation IOP in slight downgaze may be useful for addressing this issue.

The lid and orbital anatomy also have implications for choosing the type of glaucoma surgery.

“For example, placement of a drainage device may be a better option than filtration surgery in a patient who has eyelid retraction or a bulging globe relative to the orbital rim,” Dr. Radhakrishnan said.

The surgical site exposure is affected by the size of the palpebral fissure and is also a factor in choosing the type of glaucoma surgery.

For example, in patients with small palpebral fissures, minimally invasive glaucoma surgery (MIGS) that can be performed via a temporal clear corneal incision may be the preferred option rather than traditional glaucoma procedures, such as filtration surgery or drainage devices that require a larger working space posterior to the limbus.

Adequate surgical site exposure for these procedures can usually be achieved with a good corneal traction suture, Dr. Radhakrishnan said.

In patients with very small palpebral fissures who require drainage device placement, a canthotomy and cantholysis may be necessary to release the eyelid from the globe and allow access to the region 8 to 10 mm posterior to the limbus where the device plate is sutured to the sclera.

As a postoperative consideration after placing a drainage device, it may be difficult to detect a posterior erosion in patients with a tight orbit or small palpebral fissure. If infection is suspected, visualization can be improved using a lid speculum or eyelid retractor, although it may be necessary to wait a few days post-initiation of antibiotic treatment to perform the examination.

**GLAUCOMA TREATMENT-RELATED EFFECTS**

PAP is a well-known side effect of glaucoma treatment with prostaglandin analogues. In addition to horizontally tight upper eyelids, the features of PAP include upper lid ptosis, a deep upper lid sulcus, inversion of dermatochalasis, periorbital fat atrophy, periorbital fat atrophy, mild enophthalmos, inferior scleral show, and prominent lid vessels.

“According to several case reports, these findings are reversible when the prostaglandin analogue is stopped,” Dr. Radhakrishnan said.

Glaucoma medications have also been reported to cause ectropion. Dorzolamide appears to be the most common offending agent for ectropion followed by brimonidine.

According to reports in the literature, these cases of medication-induced ectropion resolve partially or completely when the causative agent is discontinued and patients are treated with a topical corticosteroid.

Glaucoma surgery can also lead to lid and orbital pathology. A serious, but fortunately rare, complication is retrobulbar hemorrhage, which can occur if a retrobulbar block is used for anesthesia.

“Surgeons must be prepared to deal with retrobulbar hemorrhage because it can quickly lead to orbital compartment syndrome with
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Managing dry eye part, parcel in care of patients with glaucoma

Strategies reduce exposure to preservatives found in topical medications, artificial tears

By Cheryl Guttman Krader

DRY EYE disease (DED) is common among patients with glaucoma, and it is an important problem to recognize and treat because DED can potentially impact multiple dimensions of patient care, said Yvonne Ou, MD.

“Dry eye is certainly the most prominent complaint of patients we see in glaucoma clinics, and it is something we need to care about because DED can lead to medication intolerance, interfere with our diagnostic evaluations, and affect the planning and outcomes of cataract and glaucoma surgical procedures,” said Dr. Ou, associate professor of ophthalmology, University of California San Francisco.

The high prevalence of DED among glaucoma patients is explained in part by the fact that DED, like glaucoma, is an age-related disease, but the risk of DED in the glaucoma population is particularly increased by chronic use of topical medications. Dr. Ou suggested that emerging novel systems for topical drug delivery that use preservative-free formulations or reduce exposure to medications and preservatives through micro-drop dosing will reduce the risk for treatment-related DED.

“In the meantime, we can help glaucoma patients today by choosing preservative-free formulations of glaucoma medications, recommending use of preservative-free artificial tears, and offering surgical solutions to reduce their medication use,” she said.

“Laser treatment might be done earlier, perhaps even as a first-line intervention, and cataract surgery and minimally invasive glaucoma surgery procedures might be a good solution for patients with early to moderate glaucoma who have DED and are intolerant of drops.”

SCOPE OF THE PROBLEM

According to various studies, at least 40% of glaucoma patients who use preservative-containing topical agents have symptoms related to DED. Review of a list of medications that can induce or exacerbate DED shows that it includes every category of drugs used to treat glaucoma, and antimetabolites that are used as adjuncts in glaucoma surgery are culprits as well.

Available evidence also shows, however, that the prevalence of DED can be reduced to about 15% by switching patients from formulations containing preservatives to products that are preservative-free.

MANAGEMENT STRATEGIES

As stated in the 2017 report from the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II), the aim of DED management is to restore the homeostasis of the ocular surface and tear film by breaking the vicious cycle that causes and perpetuates DED. The TFOS DEWS II report also outlined a management and treatment algorithm for DED that is comprised of four steps and was intended to be used taking into account DED severity and etiology.

Step 1 is comprised of generalized, conservative interventions, ie., patient education, modifications to improve the environment and address other risk factors, use of ocular lubricants, and lid hygiene. Although the use of non-preserved ocular lubricants is listed as a step 2 intervention, Dr. Ou said that she routinely recommends preservative-free ocular lubricants to her patients with glaucoma.

“There is a panoply of artificial tears on the market, and patients often ask which they should use. Authors of a recent Cochrane review concluded that the majority of over-the-counter artificial tears may have similar efficacies, and so I tell my patients to find what works for them because I don’t have a particular preference nor have I heard from other patients that one product works best,” she said.

“But I do recommend choosing a non-preserved formulation since preservative toxicity is dose-dependent and I would rather not increase preservative exposure, especially in a patient who is already using glaucoma drops.”

Recommendations for lid hygiene and warm compresses target management for meibomian gland dysfunction (MGD), which is considered the leading cause of DED. The risk for MGD, however, may be further increased in glaucoma patients because some medications (pilocarpine and timolol) have been shown to have a direct negative effect on meibomian gland epithelial cells. In addition, there is evidence of a dose-relationship between topical drop burden and extent of meibomian gland dropout.

When discussing lid hygiene with patients, Dr. Ou said she likes to use a description she heard from her colleague Marian Macsai, MD, who refers to performing an “eyelash shampoo”.

“Patients are told to gently massage and clean their eyelashes in the shower using a warm washcloth over the eyelids, adding dilute baby shampoo if needed.” Dr. Ou explained.

Other treatments listed as “step 2” in the TFOS DEWS II report include tear conservation strategies, in-office treatments for MGD, and use of anti-inflammatory/immunomodulatory agents. Step 3 adds oral secretagogues, serum eye drops, and therapeutic contact lens options. Step 4 includes longer duration use of topical corticosteroids, amniotic membrane grafts, surgical punctal occlusion and other surgical approaches.

The intranasal tear neurostimulator (TrueTear, Allergan) that is now commercially available as a treatment for DED is not listed in the TFOS DEWS II treatment algorithm because it was approved by the FDA after the report was released. Dr. Ou suggested that intranasal tear neurostimulation might be classified as a step 3 intervention considering that like the oral secretagogues, it stimulates natural tear production. In contrast to oral secretagogues, however, there is evidence that intranasal neurostimulation increases production of mucin and lipids along with the aqueous component of tears.

TAKE-HOME

› There is a high prevalence of dry eye disease among patients with glaucoma.

Management includes strategies that reduce exposure to preservatives in therapies.

YVONNE OU, MD
E: yvonne.ou@ucsf.edu
This article is based on a presentation given by Dr. Ou at the Glaucoma SymposiumCLE during Glaucoma 360. Dr. Ou has no financial interests that are relevant to the topic discussed.
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- Prevents Intraoperative Floppy Iris Syndrome (IFIS)¹
- Reduces complication rates (epinephrine comparator)²
- Decreases use of pupil-expanding devices (epinephrine comparator)²⁷
- Reduces surgical times (epinephrine comparator)²⁴,⁶,⁷
- Prevents miosis during femtosecond laser-assisted surgery (epinephrine comparator)⁵,⁸
- Improves uncorrected visual acuity on day after surgery (epinephrine comparator)²
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IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigating solution prior to intraocular use.
OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.
Systemic exposure of phenylephrine may cause elevations in blood pressure.
Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.
The most commonly reported adverse reactions at ≥ 2% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

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Exploring why UGH syndrome persists in modern IOL era
Disorder is being seen in association with other types of intraocular implants

By Cheryl Guttman Krader

**UVEITIS-GLAUCOMA-HYPHEMA**

(UGH) syndrome has declined in incidence, thanks to changes in pseudophakic intracocular lens (IOL) implantation techniques and technology. It has not yet disappeared, however, and it is being seen in association with other types of intraocular implants, said J. Michael Jumper, MD.

“UGH syndrome was first described in 1978 as a complication in eyes implanted with early generation anterior chamber IOLs that because of issues with fit and material, caused chafing of uveal tissue,” said Dr. Jumper, Retina Service Chief, California Pacific Medical Center, and a partner at West Coast Retina in San Francisco, CA.

“As the use of closed loop and iris-clipped anterior chamber IOLs declined, so did the incidence of UGH syndrome. It has been seen, however, with IOLs implanted in the sulcus and even with in-the-bag IOLs as well as with phakic IOLs and a cosmetic iris implant.”

‘Keep in mind that UGH syndrome with this etiology has been reported in normal size eyes.’

—J. Michael Jumper, MD

**CLINICAL FEATURES**

In addition to the expansion in reported etiologies for UGH syndrome, new variations in the disease itself have been described. They include UGH Plus, in which vitreous hemorrhage is also present, and incomplete posterior UGH, in which uveitis is absent, but there is posterior chamber bleeding with or without glaucoma.

Time to onset of UGH syndrome can range from weeks to years after IOL implantation. Chafing from IOL contact can lead to severe tissue trauma, including iris erosion. Uveitis develops as a result of blood aqueous barrier breakdown, and IOP becomes elevated because of pigment dispersion and recurrent hyphema.

“Collectively these events can lead to glaucoma with optic nerve atrophy and visual field loss,” Dr. Jumper said.

Presenting symptoms of UGH syndrome include intermittent blurring, intermittent whiteout of vision that is thought to be related to intermittent elevation of IOP, erythropsia (reddening of vision), pain, photophobia and injection. Potential complications include pseudophakic bullous keratopathy, vitreous hemorrhage, and cystoid macular edema.

Dr. Jumper said there are a number of entities to consider in the differential diagnosis for eyes that present with features of UGH. Chronic postoperative endophthalmitis, Fuchs heterochromic iridocyclitis and herpes viral uveitis are three such conditions that can be mistaken for UGH.

“Manifestations of herpes simplex virus infection include iris atrophy that might be mistaken for chafing, and it can certainly be associated with marked anterior segment inflammation.

**MANAGEMENT OPTIONS**

Although surgical intervention is often necessary for UGH syndrome, medical treatment to control the inflammation and glaucoma is sometimes sufficient.

“Blood, even vitreous hemorrhage, may clear spontaneously. More often, however, a need to address the IOL and to treat the glaucoma give reasons to operate,” said Dr. Jumper.

The indications for surgery include recurrent or frequent bleeding, development of glaucomatous damage, and inflammation that is refractory to medical treatment.

Surgical management of the IOL aims to eliminate contact between the implant and the uvea, and it may target either the IOL or the uvea. In some cases, the implanted IOL can be repositioned, but removal or exchange may be necessary. Techniques directed at the uvea include laser iridotomy if there is an iris bombé or cyclophotoagulation to cause retraction of ciliary processes that may be interacting with the haptic of the IOL.

**TAKE-HOME**

» Uveitis-glaucoma-hypHEMA syndrome is now rare but is being seen with a variety of intraocular implants. Retina specialist, J. Michael Jumper, MD, discusses its causes, features, differential diagnosis, and management.

**CASE EXAMPLES**

Dr. Jumper illustrated the various causes, presentations, and approaches to management for UGH syndrome by describing three cases.

The first was a 46-year-old woman who presented with recurrent loss of vision, hand motion visual acuity, and IOP of 44 mmHg 7 years after cataract surgery with in-the-bag placement of a single-piece IOL. She was a very high myope and had undergone repair for retinal detachment with a scleral buckle, gas, and endolaser treatment 27 years earlier.

On examination she had features of UGH Plus with focal iris atrophy, 5% hyphema, intraocular inflammation, and vitreous hemorrhage.

Continues on page 35: UGH syndrome
New study confirms role of Mediterranean diet in reducing AMD risk

A LARGE collaboration of researchers from the European Union investigating the connection between genes and lifestyle on the development of age-related macular degeneration (AMD) has found that people who adhered to a Mediterranean diet cut their risk of late-stage AMD by 41%. This research expands on previous studies and suggests that such a diet is beneficial for everyone, whether they already have the disease or are at risk of developing it. The new research is online (https://prn.to/2OT5dem) in Ophthalmology.

Previous research has linked the Mediterranean diet to a longer lifespan and a reduced incidence of heart disease and cognitive decline. But only a few studies have evaluated its impact on AMD. Some studies showed it can help with certain types of AMD, or only at different stages of the disease.

For this latest study, researchers analyzed food-frequency questionnaires from nearly 5,000 people who participated in two previous investigations—the Rotterdam Study, which evaluated disease risk in people age 55 and older, and the Alienor Study, which assessed the association between eye diseases and nutritional factors in people aged 73 and older.

Patients in the Rotterdam study were examined and completed food questionnaires every five years over a 21-year period, while patients in the Alienor Study were seen every two years over a 4-year period. The researchers found that those who closely followed the diet were 41% less likely to develop AMD compared with those who did not follow the diet.

They also found that none of the individual components of a Mediterranean diet on their own—fish, fruit, vegetables, etc.—lowered the risk of AMD. Rather, it was the entire pattern of eating a nutrient-rich diet that significantly reduced the risk of late AMD.

“You are what you eat,” said Emily Chew, MD, a clinical spokesperson for the American Academy of Ophthalmology, who serves on an advisory board to the research group conducting the study. “Chronic diseases such as AMD, dementia, obesity, and diabetes, all have roots in poor dietary habits.”

USH SYNDROME

(Continued from page 34)

Ultrasound biomicroscopy (UBM) showed anterior displacement of the IOL with a haptic impinging on the iris. It was determined that Soemmering ring lens proliferation caused displacement of the haptic into the iris and consequently iris atrophy.

The patient was started on oral and topical ocular hypotensive medications, and while the IOP was reduced into the 20s, the patient eventually needed to undergo vitrectomy and IOL exchange with placement of an anterior chamber lens. After surgery, but the bleeding and uveitis resolved, IOP normalized, and the patient regained good visual acuity.

UGH Plus was also the diagnosis in a 70-year-old woman who complained of blurred vision and floaters 1 year after cataract surgery with a single-piece acrylic IOL implanted in the capsular bag. She presented with 20/50 visual acuity and IOP of 21 mm Hg on maximum medical therapy.

The patient had glaucomatous optic nerve damage, inflammation, microphyma, and vitreous hemorrhage. Ultrasound biomicroscopy and gonioscopy showed that the IOL haptic was impinging on the ciliary body.

“One might expect to see ciliary body or iris irritation from the haptic of an in-the-bag single-piece IOL in a small, hyperopic eye, but keep in mind that UGH syndrome with this etiology has been reported in normal size eyes,” Dr. Jumper said.

Surgical management was undertaken, combining vitrectomy, IOL exchange with placement of a scleral-fixed spherical aberration neutral acrylic IOL (Akreos AO, Bausch + Lomb) using a polytetrafluoroethylene monofilament (Gore-Tex, Gore Medical) suture, and glaucoma tube surgery.

A third case involved a 68-year-old man with recurrent vision loss who developed incomplete posterior UGH syndrome in association with a scleral-sutured IOL.

He had a history of retinal detachment repair with pneumatic retinopexy followed by uncomplicated cataract surgery, but the IOL dislocated into the vitreous cavity 5 years later with the haptic impinging on the ciliary body. The IOL was repositioned and anchored with scleral suturing of the haptics, but the patient presented with recurrent vitreous hemorrhage and inflammation over the next 17 months.

“In a published series of six cases of incomplete posterior UGH syndrome associated with sutured IOLs, Fu et al. reported that the time to presentation ranged from 3 weeks to several years. After repair, visual acuity was 20/70 or better in five patients and hand motion in the sixth individual who had age-related macular degeneration,” Dr. Jumper said.
HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

**IMPORTANT SAFETY INFORMATION**

**SERIOUS INFECTIONS**

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB.** Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.

- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosys, and pneumocystosis.** Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.

- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.** Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- **Do not start HUMIRA during an active infection, including localized infections.**

- **Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.**

- **If an infection develops, monitor carefully and initiate appropriate therapy.**

- **Drug interactions with biologic products: A higher rate of serious infections has been observed in rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.**

**MALIGNANCY**

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to the use of a TNF blocker or a TNF blocker in combination with these other immunosuppressors.

- **Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.**

- **In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.**

- **Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.**

- **In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.**

- **Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas, other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.**

**HYPERSENSITIVITY**

- **Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.**

**HEPATITIS B VIRUS REACTIVATION**

- **Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.**

- **Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.**

- **Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.**

- **Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.**

**NEUROLOGIC REACTIONS**

- **TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain–Barré syndrome.**

- **Exercise caution when considering HUMIRA for patients with these disorders: discontinuation of HUMIRA should be considered if any of these disorders develop.**

- **There is a known association between intermediate uveitis and central demyelinating disorders.**

**HEMATOLOGIC REACTIONS**

- **Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.**

- **Consider stopping HUMIRA if significant hematologic abnormalities occur.**

**CONGESTIVE HEART FAILURE**

- **Worsening or new onset congestive heart failure (CHF) may occur; exercise caution and monitor carefully.**

**AUTOIMMUNITY**

- **Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.**

**IMMUNIZATIONS**

- **Patients on HUMIRA should not receive live vaccines.**

- **Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.**

- **The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA in utero is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.**

**ADVERSE REACTIONS**

- **The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.**


Please see Brief Summary of full Prescribing Information on the following pages.
Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal and/or retinal vascular lesions.

For adult patients with non-infectious (NI) intermediate, posterior, and panuveitis:

NON-INFECTIONOUS (NI) UVEITIS* CAN BE HARD TO CONTROL.

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*Intermediate, posterior, and panuveitis.

†Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal and/or retinal vascular lesions.
Tuberculosis
Causes of reactivation of tuberculosis and new asylum tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received tuberculosis treatment, previous history of latent tuberculosis infection, or concomitant use of your intramuscularly, discontinue tuberculosis. Evaluate patients for tuberculosis risk factors, including prior history of active or latent tuberculosis infection, and concomitant use of immunosuppressants or corticosteroids. Consider tuberculosis prophylaxis for patients at risk of tuberculosis. Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be given. See Precautions. Consultation with a physician with expertise in the diagnosis and treatment of tuberculosis is recommended in the diagnosis and treatment of tuberculosis.

Infective endocarditis
Infective endocarditis has been reported in patients with rheumatoid arthritis (RA). The concomitant use of a TNF blocker and abatacept or anakinra was associated with reduced treatment of latent tuberculosis infection prior to therapy with TNF-blocker agents has been shown to reduce the risk of tuberculosis. Always it is not known how the underlying disease. Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be given. See Precautions. Consultation with a physician with expertise in the diagnosis and treatment of tuberculosis is recommended in the diagnosis and treatment of tuberculosis.

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In controlled Phase 3 trials of HUMIRA (initial doses of 40 mg and 80 mg, or 40 mg and 20 mg on Days 1 and 5, respectively), followed by 40 mg every other week in adult patients with Ps, with methotrexate (MTX) (patients treated with the maximum recommended human dose (MRHD) of 40 mg subcutaneous without the MRHD of 20 mg subcutaneous), the incidence of adverse events was 22% and 24%, respectively. A total of 22% of patients treated with HUMIRA in controlled clinical trials had antibody development compared to 20% of patients treated with placebo. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibody development in adults with rheumatoid arthritis (RA) in controlled clinical trials. The studies were controlled clinical trials and open-label extension studies. The data for the patients treated with placebo are based on post hoc analysis that used an assay which could measure an anti-adalimumab antibody titer in all patients, whereas most patients treated with placebo did not have antibody development tested. No correlation of antibody development to safety or efficacy outcomes was observed.

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PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA “Medication Guide” to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

• Infections
Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.

• Malignancies
Counsel patients about the risk of malignancies while receiving HUMIRA.

• Allergic Reactions
Advise patients to seek immediate medical attention if they experience any symptoms of an allergic reaction. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.

• Other Medical Conditions
Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or petechial hemorrhage.

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Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through RA-IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of severe infections and malignancy among HUMIRA-treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.
In the video game, users must find the correct shape of a certain color among a range of competing colors and shapes; the shapes are in different positions on the screen and are led by an animated avatar.

“The aim of the game is to offer a colorful, engaging ‘training’ through playing the computer game—an activity which is often not viable for children with functional vision problems because of complications viewing screen graphics,” according to a statement from the University of Lincoln.

Users must find the correct shape of a certain color among a range of competing colors and shapes; the shapes are in different positions on the screen and are led by an animated avatar. One example: Players must find the orange circle that is not flashing on a screen that shows several green squares and one orange circle, all against a black background. Players receive verbal encouragement as they select the correct shape.

Game developers worked with students who have visual impairments and therapists at WESC to develop a training program that would maximize accessibility and engagement.

“The core principles of visual search training are still evident when playing Eyelander, but they are couched in game elements such as progress mechanics, simple aesthetics, narrative, and music,” Dr. Waddington said.

Users of Eyelander (available at eyelander.co.uk) are younger people with hemianopia as well as other forms of visual field loss caused by brain injury and brain dysfunction, Dr. Waddington said.

“It is too early to say whether Eyelander could be helpful for people with other visual impairments, but investigations in this area are ongoing,” he said.

The statement estimates that there are 25,800 blind and partially-sighted children in the U.K. and that cerebral visual impairment is the most common cause of blindness and visual impairment in the U.K. and other developed countries.

**GAME ON: TECHNOLOGY DESIGNED TO IMPROVE VISUAL SEARCH ABILITY**

Video game helps youth with cerebral visual impairment

*By Vanessa Caceres*

In the quest to help children with visual field loss caused by cerebral visual impairment, researchers in the United Kingdom have designed the game Eyelander.

The game uses the same concepts applied in adult stroke patients with hemianopia, said Jonathan Waddington, PhD, a computational neuroscientist for WESC Foundation in Exeter, United Kingdom. WESC Foundation is a specialist school for visually impaired children.

“We wanted to investigate whether these training programs could benefit children and young people,” said Dr. Waddington, who designed the game along with Timothy Hodgson, professor of cognitive neuroscience, School of Psychology, University of Lincoln, Lincoln, UK. The game was developed by the University of Lincoln and WESC Foundation.

The game developers knew they had to design something that would be more engaging for young users. They point out that existing training programs often are in black and white and have limited interaction.

“The aim of the game is to offer a colorful, engaging ‘training’ through playing the computer game—an activity which is often not viable for children with functional vision problems because of complications viewing screen graphics,” according to a statement from the University of Lincoln.

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**HOW GAME MAY HELP**

Playing Eyelander may not improve visual function itself, but it does have other benefits.

“Eyelander is designed to promote compensatory strategies that could improve functional vision,” Dr. Waddington said. “We don’t expect training with Eyelander to improve the area of the visual field itself. Instead, we expect changes in visual attention and eye move-
Optic atrophy in children: Taking aim at possible hereditary atrophies

Screening recipes should ease the diagnostic burden in this patient population

By Lynda Charters; Reviewed by Nancy J. Newman, MD

DIAGNOSING OPTIC atrophy in children is a complicated business, but what confounds the situation even more is that the inherited optic neuropathies are only one of a plethora of causes of optic atrophy in children, said Nancy J. Newman, MD.

“In addition to the inherited causes of optic atrophy, clinicians still need to think about all the other causes of optic atrophy,” said Dr. Newman, the LeoDelle Jolley Professor Ophthalmology, Emory University School of Medicine, Atlanta.

A pearl that she offered physicians underscores the importance of magnetic resonance imaging of the brain and orbits with and without gadolinium when evaluating a child with optic atrophy but not necessarily with congenital nystagmus.

In this clinical scenario, she also advised ordering tests for neurofilosllsions optica and myelin oligodendrocyte glycoprotein antibodies, checking the medication list for any toxicities such as any antibiotics having been prescribed, ascertaining any toxic exposures, and finally consideration of nutritional deficiencies.

Another big must for Dr. Newman especially in the presence of a syndrome is the consideration of a retinal cause despite the fact that the optic nerves appear pale.

“Always order an electroretinogram,” she said.

FERRETING OUT CORRECT INHERITED OPTIC ATROPHY Physicians used to approach this task by using linkage analysis in large families affected with a specific disease. This might possibly lead to identification of the affected gene(s).

More recently than linkage analysis, syndrome recognition with targeted gene sequencing based on a possible syndrome has been useful to clinicians.

Dr. Newman provided the example of such a case in a 5-year-old boy of Iraqi Jewish descent who had development delay, spasticity, and severe visual loss with nystagmus and optic atrophy. Urine analysis showed elevated 3-methylglutaconic acid levels. The patient’s older sister has a similar disorder, but five other siblings do not. The parents are first cousins. The child was diagnosed with Costeff syndrome after screening of the OPA3 gene on chromosome 19.

Most recently, Dr. Newman explained, that syndrome recognition is no longer necessary because of the availability of gene panel screening for optic atrophy and full genome sequencing.

She demonstrated how this syndrome recognition worked in the case of a 15-year-old healthy boy in whom bilateral painless visual loss developed over the course of 1 month. The visual acuity was counting fingers, and the first examination showed large central scotomas. The optic nerves have some hyperemia and telangiectasia.

Three months later, he has optic atrophy. The pedigree showed the affected relatives on the maternal side.

The diagnosis was Leber’s hereditary optic neuropathy (LHON), which is characterized by sequential bilateral central visual loss, usually legal blindness, onset most often from 15 to 35 years of age, male predominance, and in 90% of cases due to three predominant mutations in the mitochondrial DNA. Numerous other mutations in the mitochondrial DNA also have been identified.

Interestingly, LHON can recover spontaneously years after the diagnosis, most often the case with the 14484 mitochondrial DNA mutation. Recovery also is more likely when the visual loss occurs before the patient is 20 years of age and especially if the child is younger than 10 years.

A second example of syndrome recognition is the case of a 7-year-old girl who was found to have 20/100 vision bilaterally during a school eye examination.

Further examination showed the presence of cecocentral scotomas and wedges of optic atrophy. The family history indicated that the father has slight paliors of the optic nerves. The child was diagnosed with dominant optic atrophy, insidious onset in the first decade of life, visual function that is not as bad as LHON, mild symmetric progression, and moderate color defects.

The gene for this disorder is on chromosome 3, which also codes for a mitochondrial protein. “Ninety percent of the proteins necessary for mitochondrial function actually are coded for in the nucleus and they make their way into the mitochondria. Therefore, mitochondrial diseases can develop even from nuclear DNA abnormalities or mitochondrial DNA abnormalities,” Dr. Newman said.

DIDMOAD, Wolfram’s syndrome, is another recognized syndrome that is associated with juvenile diabetes mellitus and diabetes insipidus, as well as sensorineural hearing loss and severe optic atrophy.

The onset of visual loss is from 5 to 21 years of age. Other associated findings that make the physician think about mitochondrial dysfunction include but are not limited to ataxia, seizures, mental retardation, nystagmus, ptosis, and short stature.

This disorder is very heterogeneous, which continues on page 44: Atrophy
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More recently than linkage analysis, syndrome recognition with targeted gene sequencing based on a possible syndrome has been useful to clinicians.

The first was that of an 8-year-old boy with slowly progressive visual loss bilaterally and optic atrophy who turned out to have LHON.

A case of a 42-year-old man was incidentally found to have optic atrophy and 20/40 bilateral vision; he was diagnosed with dominant optic atrophy.

A third case was that of a 16-year-old girl who had progressive loss of hearing from the age of 2 years who was incidentally found to have optic atrophy with normal vision; she had Wolfram’s syndrome.

The last case was a 15-year-old boy from the UK with several weeks of vision loss bilaterally and optic atrophy that turned out to be biotinidase deficiency that was not screened for when he was a newborn.

She said and advised knowing what optic atrophy panels are available.

Regarding metabolic panels she advised clinicians to know the newborn screening strategies of their home countries and states as well as the birth place of the newborn.

Another important treatment strategy is partnering with a pediatric neurologist and geneticist.

Finally, because mitochondrial dysfunction plays such a big role in some of these disease, Dr. Newman urged clinicians not to forget about other causes of optic atrophy even if they are convinced the disease is inherited. These other causes of optic atrophy also can arise from mitochondrial dysfunction, such as nutritional, metabolic, or toxic abnormalities that could have triggered a disorder in patients with an underlying mutation.

Andrew G. Lee, MD, professor of ophthalmology, neurology, and neurosurgery, Institute for Academic Medicine, and chairman, Blanton Eye Institute, Houston Methodist Hospital, Houston, believes that video games such as Eyelander are a reasonable way to help visual function and to engage patients with visual field defects. However, keeping users—especially children—interested in such a game is crucial.

“Motivation is a key to sustainability and gamifying the rehab effort is an interesting strategy for kids, especially in this high-tech, wired environment. The drawbacks are the same for any video game format in terms of time, attention, and prioritization,” Dr. Lee said.

With a parent’s permission, data can be collected from current Eyelander users to help inform the design of a randomized controlled trial, Dr. Waddington said.

Also, children at the WESC Foundation are playing the game, which will help researchers gather more data.

More games similar to Eyelander will likely be developed in the future, Dr. Lee believes.

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Low dose atropine may slow myopia progression in certain children

Level of evidence is decent, but may not be applicable to all racial, ethnic groups

By Fred Gebhart; Reviewed by Stacy Pineles, MD

The causes of pediatric myopia are still a mystery. While genetic factors likely play a role, the transition from outdoor activity with visual focus at ever-changing distances to close vision activities seems to be a contributor. And there is growing evidence that atropine can slow progression in children with myopia, she noted.

“Myopia is becoming an epidemic as kids are becoming more and more nearsighted at a younger age than they used to,” said Stacy Pineles, MD, associate professor of ophthalmology at the Stein Eye Institute, David Geffen School of Medicine, University of California, Los Angeles.

“Not only does it mean more kids need glasses earlier in life, but myopia can lead to more serious eye diseases, including glaucoma, cataracts, retinal detachment and myopic maculopathy,” she added.

Dr. Pineles reviewed the latest data on the use of atropine to slow or stop progression of childhood myopia. She is the lead author of an AAO Ophthalmic Technology Assessment report published last year.

The OTA group found 98 citations in the literature, reviewed 23 articles and included 18 articles in its assessment. Most of the studies conducted to date have been done in Asian populations, she noted, but trials conducted in the United States in other racial and ethnic populations show similar results.

Along with cataract, glaucoma, trachoma and onchocerciasis, myopia is one of five conditions identified as an immediate priority by the World Health Organization’s Global Initiative for the Elimination of Avoidable Blindness, she noted.

Myopia remains the most common medical condition requiring treatment in developed countries. It affects about half the adult population of the United States and the pediatric prevalence has jumped from 25% to 42% over the past 30 years. Myopic maculopathy is one of the top five causes of blindness in the United States, UK, Ireland and Israel.

Rates are even higher in Asia, Dr. Pineles said. The prevalence of myopia doubled in Singapore from 1987 to 1992 and again from 1992 to 2009. Myopic maculopathy is the second most common cause of low vision in Beijing.

The causes of pediatric myopia are still a mystery, she added. While genetic factors likely play a role, the transition from outdoor activity with visual focus at ever-changing distances to close vision activities such as reading and screen use seems to be an important contributor. And there is growing evidence that atropine can slow progression once myopia is identified in certain cases.

Atropine is clearly more effective at controlling myopia in children compared to single vision lenses or placebo, Dr. Pineles noted, at least in the short term. The mechanism of action remains unclear.

Early studies suggested that atropine has an effect on lens accommodation. Later studies suggested an effect via an undetermined non-accommodative pathway in the retina or sclera.

Newer theories suggest that pupillary dilation may result in increased ultraviolet A exposure, which may limit axial elongation. Another theory suggests that myopia may be associated with increased chronic inflammation of the eye which could be down regulated by atropine.

Early clinical trials in atropine in children with myopia suggested a dose-dependent response in myopia progression versus pupil size and accommodations. Those early findings led to trials in Singapore, Taiwan, and other countries comparing different doses against single vision and progressive lenses.

Most of the trials used atropine 1%, which produced significant side effects. Problems included pupil dilation and blurred close vision.

The most troubling adverse event was rebound myopia when treatment was halted.

“There was a concerted effort to create studies that evaluated lower doses of atropine that might decrease the risk of side effects and decrease the rebound effect,” Dr. Pineles said.

A 2012 trial of 400 children in Singapore, ATOM2, added atropine 0.5%. Poorer outcomes in placebo arms of earlier studies convinced researchers and review boards that continuing to include a placebo group would be unethical, so researchers added a 0.01% formulation to the trial design.

The results, published in 2016, were a surprise, Dr. Pineles said.

Of the children in the 0.01% group, only 6% requested reading glasses compared to 70% in the 0.5% group and 61% in the 1% group. The very low dose group had the best balance of clinical efficacy with slightly more progression of myopia compared to the other arms but less rebound and an improved side effect profile.

“The use of atropine to slow myopic progression in children is still experimental, Dr. Pineles said.

The level of evidence we have is decent, but may not be applicable to all racial and ethnic groups, she said.

“We just don’t have enough results so far to know,” Dr. Pineles added. “For now, I would keep it in mind for my patients who seem to be progressing rapidly enough that you are having concerns about them reaching a level of myopia that might be considered dangerous. We may not have perfect evidence, but it is something you can discuss with the parent.”
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Rebound tonometry useful tool to measure IOP in children

Device is noninvasive, nonthreatening; does not require topical or general anesthesia

By Fred Gebhart

MEASURING INTRAOCULAR pressure in children is a challenge. So much of a challenge that many ophthalmologists do not bother in the absence of any signs or symptoms suggesting there may be a problem. A relatively new method of assessing IOP, rebound tonometry, can ease the burden.

“What used to happen is that intraocular pressure was rarely checked in young children because it is such a difficult thing to do,” said Scott R. Lambert, MD, professor of ophthalmology and pediatrics at Stanford University School of Medicine. “When we absolutely had to check the intraocular pressure, in most cases we had to take them to the hospital and do it under general anesthesia.

“With rebound tonometry, we now check IOP on virtually every child that comes in for an exam, even if they don’t have a known problems with intraocular pressure when they come in,” he said. “Measuring IOP is such a simple thing to do with this technique.”

That was before pediatricians, ophthalmologists, anesthesiologists and the FDA recognized that repeated use of general anesthesia may affect the neurodevelopment of young children. And before Finnish medical device maker iCare developed the first rebound tonometer.

Unlike Goldman applanation, Kowa, Tono-pen and non-contact air puff devices, rebound tonometry is noninvasive, nonthreatening, does not require topical or general anesthesia and can be used at any age.

“I had a patient come in recently with glaucoma who was two weeks old and I could check the intraocular pressure in this child with rebound tonometry,” Dr. Lambert said. “It has really changed how we manage these children.”

Take-home
Rebound tonometry is a disruptive technology for checking IOP in children. It has tremendous penetration in pediatric ophthalmology practices around the world, notes Scott R. Lambert, MD. The device bounces a small, lightweight disposable probe off the cornea.

VALUE AS SCREENING INSTRUMENT
The AAO technology assessment group assessed the outcomes of four pediatric studies. The group found that rebound tonometry tended to measure 2–3 mm Hg higher than Goldman applanation tonometry. Differences between the two techniques were greater at higher pressures.

“Rebound tonometry is a great screening tool,” Dr. Lambert said. “If you get a high pressure from rebound tonometry, you need to follow up with some other test. But if the pressure is normal, you can be pretty confident that the child’s IOP is okay and no other testing is needed.

The group also noted that rebound tonometry is better tolerated than applanation tonometry in young children.

Cost is also considerably lower for rebound tonometry. Each rebound tonometry measurement costs a few dollars versus a few thousand dollars for each an exam-under-general anesthesia.

Ophthalmologists were reluctant to subject children to an exam-under-anesthesia unless an IOP reading was absolutely necessary even before the recognition that extended or repeated general anesthesia may affect the developing brain. Hospitalization was traumatizing to child and family as well as expensive.

As a result, a small subset of children with known glaucoma or other IOP abnormality were subjected to general anesthesia 20 to 30 times during childhood. And most children never had their IOP measured.

It has long been recognized that many children will develop glaucoma following cataract surgery, Dr. Lambert noted, but the pathogenesis of glaucoma in this population has been largely unknown because IOP was rarely measured after pediatric glaucoma surgery.

“In many cases, glaucoma following congenital cataract surgery was reported to develop at older ages,” he explained, “but I think that was because they just didn’t have the ability to check IOP easily and regularly while they were young. Rebound tonometry is giving us more information about the natural history of glaucoma following pediatric cataract surgery because we can now check IOP throughout childhood. It is helping us to understand the disease better and to treat at the most appropriate time rather than after they have more advanced disease.”
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By Michelle Dalton, ELS; Reviewed by Daniel Simhaee, MD, and Ajay E. Kuriyan, MD, MS

Commercial cell therapy clinics yield little evidence

Researchers found limited publications and dearth of information about side effects

By Michelle Dalton, ELS; Reviewed by Daniel Simhaee, MD, and Ajay E. Kuriyan, MD, MS

Promising results from several clinical trials have piqued interest in stem cell therapy. In a phase I/IIa multicenter trial for patients with geographic atrophy secondary to age-related macular degeneration, those who were given subretinal injections of human umbilical derived stem cells noted a “significant increase in vision and central macular thickness: 33 eyes were studied, and at 1 year 35% gained 10 letters or more, and 25% gained 15 letters or more (but had a high risk or retinal perforation/detachment),” said Daniel Simhaee, MD, University of Rochester Medical Center.

However, there are no cell therapies approved by the FDA. That has not deterred some commercial clinics from offering “cell therapy” treatments to patients directly. Ajay K. Kuriyan, MD, MS, University of Rochester Medical Center’s Flaum Eye Institute, treated patients who had undergone bilateral experimental cell injections at one of those clinics. Three patients developed severe bilateral visual loss after they received intravitreal injections of autologous adipose tissue-derived “stem cells.”

In these three patients, the last documented visual acuity on the Snellen eye chart in their better-seeing eye before the injection ranged from 20/30 to 20/50. The patients’ severe visual loss after the injection was associated with ocular hypertension, hemorrhagic retinopathy, vitreous hemorrhage, combined traction and rhegmatogenous retinal detachment, or lens dislocation. After 1 year, the patients’ visual acuity in their better-seeing eye ranged from 20/200 to no light perception.1

“We thought that these were the only cases that existed, but after our publication,1 we found several other patients at different clinics that also had similar poor outcomes,” Dr. Kuriyan said.

That led to trying to determine “what the scope of these cell therapy clinics are and we were amazed to find out that there’s about 40 different cell therapy clinic sites just in the U.S. alone. And these sites are advertising to consumers directly about their potential benefits and often times, we found on these websites, that there are vague claims about what they can offer and what they can do for different retinal diseases,” he said.

WHAT THE EVIDENCE SAYS

The group performed a comprehensive literature search to ascertain what Level of Evidence existed for treatments of retinal diseases at these “cell therapy” clinics and “we basically found a paucity of publications,” Dr. Simhaee said. “There were no publications that had Levels 1 through 4 evidence based on the Oxford Centre Level of Evidence, and only one with Level 5. There was one case report of a patient who had serpiginous choroidopathy, which was treated with bone marrow stem cells, and was reported to have some improvement in vision.”

But there were multiple publications that disclosed severe visual complications (one Level 4 Evidence, and two with Level 5 Evidence). Beyond those reported by Kuriyan et al.,1 Dr. Simhaee found others. Given the lack of published data, Dr. Simhaee evaluated the stem cell clinics’ websites to determine what risk/benefits the clinics are promoting.

“We found a total of 23 clinics that provide stem cell therapy for retina conditions,” Dr. Simhaee said. “Nearly half claimed there would be clinically significant benefits, and only 10% explicitly stated those benefits are not guaranteed. That’s really what made us concerned. This is the information patients are getting, and they’re not really being educated on the very real risks of these unapproved procedures.”

EDUCATING PATIENTS ABOUT RISKS

Legitimate clinical trials are under way, Dr. Simhaee said.

“Those studies are reported in reputable journals and have a fair amount of patients enrolled in the clinical trials with safety oversight. So, frankly, I was not surprised when we went to the commercial stem cell center websites and were unable to find hard data,” he said.

“Cell therapy has a lot of promise for ophthalmology and these legitimate studies show the potential,” Dr. Kuriyan said. “We’re very eager to see results in a larger number of patients and over a longer period of follow up, but we still have to wait to see them before we can make a full judgment.”

Studies alerting consumers to the potential for unregulated cell therapy and the potential for poor outcomes need to be communicated to the public, he added.

Part of patient communication is that legitimate studies are often sponsored by either government or companies, will not ask for payment out-of-pocket, and will likely not bilaterally inject before they can show good safety data.

“If the only service a place offers is cell therapy treatments, that’s also a red flag,” Dr. Kuriyan said. “Alerting patients that they should be asking about all treatment options, including observation. If a center does not offer anything beyond cell therapy injections, they may not be legitimate.”

TAKE-HOME

Researchers are assessing the level of evidence for commercially available cell therapy treatments for retinal diseases at cell therapy clinics within the United States.

Reference


Daniel Simhaee, MD

p: 585/276-3000

This article was adapted from Dr. Simhaee’s presentation at the 2018 meeting of the American Society of Retina Specialists. Drs. Simhaee and Kuriyan do not report any financial disclosures.

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Anti-VEGFs can improve DRSS in majority of patients

Study results show ~60% improvement by ≥2 steps after intravitreal aflibercept

By Michelle Dalton, ELS

**USING A SPECIFIC anti-vascular endothelial growth factor (VEGF) drug in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) can result in a ≥2-step improvement in diabetic retinopathy severity scores (DRSS) in almost 60% of those treated, according to results of the PANORAMA study presented during this year’s American Society of Retina Specialists meeting. These study results add to the ever-growing body of evidence that suggest anti-VEGF injections can lead to “robust” improvements in diabetic retinopathy, one expert notes.**

In fact, the 2018 PAT Survey 1 found intravitreal anti-VEGF agents are the overwhelming first choice by retina specialists for treating diabetic eye diseases.

In the early 1990s, the Early Treatment of Diabetic Retinopathy Study standardized how to quantify and qualify NPDR and created a threshold for its treatment, Dr. Wykoff said. “That standardization allowed different researchers and clinicians to begin to speak the same language about DR but maybe even more importantly, the designation of an eye within this quantitative scale has proven to be predictive of DR progression itself,” he said.

Greater DR scores confer a greater chance of converting to PDR, he added.

Higher scores are also associated with decreased vision-related quality of life measures, he said, making earlier intervention a key component to consider in management. “Patients with center-involved diabetic macular edema (DME) with visual acuity loss warrant intervention,” he said. “Those with high-risk PDR warrant intervention as well.”

But other scenarios are not as clear cut such as patients with non-center involved DME and those with center-involved DME but without specific visual acuity loss, according to Dr. Wykoff. “But what about nonproliferative disease?” he said. “There is little data available to guide discussion on when to treat these patients and how often.”

To that end, Dr. Wykoff and colleagues wanted to evaluate “the efficacy and safety of intravitreal aflibercept injection for treatment of moderately severe to severe NPDR in eyes that had not yet developed DME.”

As the results of the PANORAMA study showed, Dr. Wykoff and colleagues wanted to evaluate “the efficacy and safety of intravitreal aflibercept injection for treatment of moderately severe to severe NPDR in eyes that had not yet developed DME.”
The PANORAMA trial is a phase III, double-masked, randomized study with a primary outcome at week 24 of the proportion of patients who improved by at least 2 steps on the DRSS (ClinicalTrials.gov Identifier: NCT02718326). The study enrolled 402 patients with NPDR without DME and a DRSS score of 47 or 53. Patients were randomized to two dosing schedules of intravitreal aflibercept (2 mg every 8 weeks or every 16 weeks) or to sham injection.

The primary endpoint was the proportion of patients with a ≥2-step improvement in DRSS score from baseline to 24 weeks. The two aflibercept groups were combined for the primary outcome analysis.

Baseline demographics were similar among the three groups, with a mean age of 56, mean A1c of 8.5%, and mean diabetes duration of 14 years. Baseline vision averaged between 82 and 83 letters, and the mean central retinal thickness was 246-249 μm.

At week 24, 61.5% of those in the 8-week aflibercept group (83/135) and 55.2% in the 16-week aflibercept group (74/134) had a ≥2-step improvement from baseline in DRSS, compared to 6% in the sham group (8/133).

Almost 10% of the aflibercept-treated eyes had a ≥3-step improvement in DRSS scores compared to <1% of the sham group. Vision improved slightly in the aflibercept groups, with each gaining 1.9 letters compared to the sham group, which gained 0.4 letters.

Central retinal thickness improvements also were statistically significant greater for aflibercept, with the pooled group improving by ~19.4 μm compared to the sham group, which increased in thickness by 4.7 μm.

About 25% of the sham group developed vision-threatening complications, including PDR/center-involving DME (14.4%). The pooled aflibercept groups had a cumulative rate of vision-threatening complications of 4.5%.

Otherwise, there were no new safety signals, Dr. Wykoff said.

Other anti-VEGFs have also demonstrated efficacy toward DR severity improvement. A post hoc analysis of the RIDE and RISE studies (n = 468) found “further support that improvement in DRSS is a clinically important outcome that should be evaluated as a measure of treatment effectiveness in future studies of diabetic eye disease.”

Similarly, treatment with intravitreal ranibizumab can improve DRSS by 2 steps at year 2 in 37% of patients treated and in up to 39% of patients treated in year 3.

Treatment with aflibercept has shown a ≥2-step or more improvement in DRSS (29.3%-37.1%) in patients with confirmed DME at 100 weeks in another study.

While the decision to treat these patients should remain individualized, “the PANORAMA study has provided excellent data to guide the discussion,” Dr. Wykoff said.

References

CHARLES C. WYKOFF, MD, PhD, is a consultant for Allergan, Alimera, Bayer, Clearside, DORC, Genentech, DME, Therapeutics, and Regeneron.
New horizons in pharmaceuticals
Therapies are targeting the trabecular meshwork, Schlemm’s canal for treatments
By Fred Gebhart

FROM RECENT FDA drug approvals in glaucoma to the newest research, conventional drainage outlets are back in vogue. The trabecular meshwork and Schlemm’s canal have gone from familiar anatomical features to the most popular druggable targets researchers and industry have seen in years.

AERIE PHARMACEUTICALS
Aerie is enlarging its footprint in ophthalmology and is doing it in glaucoma. The FDA approved Rhopressa, the company’s first in class rho kinase inhibitor, in late 2018. With an initial indication in hand, Aerie is looking to take the agent even farther.

“About 60% of U.S. glaucoma patients are diagnosed at an IOP below 21 mm Hg,” said President and Chief Executive Officer Tom Mitro. “That is a major unmet need in glaucoma today. We know that Rhopressa is as effective at lower pressures as at higher pressures and lowers IOP equally well daytime and nighttime. Both are major improvements over existing medications and we should be pursuing those areas in the future.”

Continuing research also shows that Rhopressa has anti-fibrotic activity in the trabecular meshwork, Mitro continued. Fibrosis in the trabecular meshwork leads to stiffness, increased resistance to flow and higher IOP.

ALLYSTA PHARMACEUTICALS
Rho is not the only kinase that plays a role in trabecular meshwork outflow and regulating IOP. Multiple kinases are involved. Which is why Allysta and Japanese research partner D Western Therapeutics Institute are testing a multi-kinase inhibitor dubbed H1337.

“In addition to rho kinase, H1337 hits novel targets, including leucine-rich repeat kinase (LRRK), myosin light chain kinase, PTK1 and PKA,” said Allysta Founder and Chief Executive Officer Henry Hsu, MD.

LRRK is a novel target in glaucoma but is well-described in Parkinson’s, where overexpression disrupts cellular structure to an inherited form of the disease. In the eye, LRRK disrupts the cytoskeleton in the trabecular meshwork, inhibiting outflow. In animal models, H1337 is significantly more effective than latanoprost in reducing IOP.

Allysta launched phase II trials of H1337 earlier this year in POAG. Dr. Hsu said early human data should be available sometime in December.

BAUSCH + LOMB
Bausch + Lomb is also targeting the trabecular meshwork with its recently approved glaucoma drug, Vyzulta, the first nitric oxide donating prostaglandin. The active ingredient, latanoprostene bunod, hydrolyzes into latanoprost acid and nitric oxide.

“Just like vascular endothelia cells, trabecular meshwork cells undergo skeletal changes in response to nitric oxide,” said Robert Kissling, vice president of medical affairs. “The trabecular meshwork cells relax, allow increased spacing between the cells, increasing outflow and decreasing pressure.”

Latanoprost acid acts on the uveoscleral pathway.

The dual mechanism of action gives Vyzulta greater IOP reductions than timolol. Pooled data from the two U.S. pivotal trials showed a 32% mean reduction in diurnal IOP. Fewer than one percent of trial participants discontinued therapy due to ocular events, primarily ocular hyperemia, conjunctival irritation and other side effects commonly seen in prostaglandins.

GLAUKONIX BIOSCIENCES
Glukonix is about technology, not product. The company grew out of the recognition that glaucoma researchers see a 90% failure rate in clinical trials compared with 50% in cardiovascular disease.

“Areas like cardiovascular disease and oncology are dealing with breakthroughs in biologics, novel immune therapies and delivery systems while glaucoma moves at a more incremental pace,” said Karen Torrejon, PhD, founder and chief science officer. “These other areas have embraced novel biotechnologies that are allowing them to explore novel therapies much faster than in glaucoma and with much lower risk.”

Glukonix provides a novel three-dimensional human tissue model that allows researchers to mimic the trabecular meshwork, Schlemm’s canal, and other ocular structures. The model can compare healthy tissue to glaucomatous tissue to model the effects of changing IOP, gene expression, protein markers and other elements.

Glucoma is the first target disease, Dr. Torrejon noted, the trabecular meshwork and Schlemm’s canal the first model human tissues. But the technology is tissue agnostic, Dr. Torrejon noted, and can model the anterior chamber, posterior chamber and any ocular structure to test potential drugs, biologics, gene therapy, devices or combination products.

LYMPHATIC THERAPEUTICS
Aqueous humor is not a unique fluid. It bears many similarities to lymphatic fluid. Both fluids originate in the circulation, neither contains red blood cells, and both return to circulation through the venous system.

“Many diseases inside and outside the eye are associated with lymphatic disorders, from inflammation and infection to dry eye and graft rejection,” said Chief Scientific Officer Lu Chen, MD, PhD. “After 15 years of ophthalmic lymphatic research, we have developed highly useful models of Schlemm’s canal and a major focus on pharmaceutical research.”

Making the connection between the lymphatic and ocular systems was a fortuitous accident, “Dr. Chen said.

While trying to visualize lymphatic vessels, researchers noticed another large structure exhibiting the same markers. It turned out to be Schlemm’s canal.

Working in mouse models, her lab developed technologies to not only visualize Schlemm’s canal, but modulate IOP and other factors and visualize resulting changes at the cellular and protein expression level.

A novel molecule allows manipulation of cell proliferation, adhesion, formation and other functions that can be adjusted to open up space in Schlemm’s canal and increase outflow.
Drug delivery removes adherence from equation, but raises new issues

Concerns exist over how reliable is duration of action; when to renew therapy

By Fred Gebhart

GLAUCOMA TREATMENT is a paradox: Clinicians have highly effective treatments, but patients do not take their medications appropriately. Sustained-release drug delivery takes the patient out of the adherence equation, but raises new issues, noted James D. Brandt, MD, professor and director, Glaucoma Service, at the Tschenen Eye Institute, University of California, Davis. Dr. Brandt co-moderated the New Horizons session on drug delivery earlier this year at the Glaucoma 360 meeting.

How reliable is the duration of action? Is it precisely six months? How will clinicians and patients know when to renew long acting therapy? Will home tonometry monitoring help?

Will the device or platform deliver multidrug therapy? And because glaucoma is usually bilateral, how will the need for bilateral injections or device implantation affect clinicians’ office workflow? How many injections or implantations can the cornea take without exhibiting changes in endothelial cell counts and other deleterious effects?

Most devices and platforms can answer at least one of these questions. A growing number can address multiple potential problems.

“The demise of eye drop therapy is exaggerated,” said James D. Brandt, MD, but the pace of innovation suggests that drops are not going to be the primary way of treating glaucoma a decade from now.”

EYENOVIA
Eye drops are far from ideal, but the ocular surface remains an alluring target. Eyenovia aims to avoid the pitfalls of eye drop administration.

“One of the solutions is Eyenovia, a micro-dosing device based on piezoelectric technology, a very fine application of spray, very localized,” said company consultant Shan Lin, MD, Professor of Clinical Ophthalmology at the University of California, San Francisco. “The device can reduce the dose from the 40 to 50 mL we typically see in an eye drop to about seven milliliters, close to the lowest effective dose and reducing overexposure to drug three- to seven-fold.”

The device delivers a very fine, highly focused spray so quickly that the entire dose is delivered faster than the patient can blink. Based on mydriasis studies using phenylephrine, Eyenovia spray is as effective as 10 percent eye drops with fewer adverse effects.

Trials in primary angle closure glaucoma are slated to begin later this year,” Dr. Lin said, followed by trials in open angle glaucoma. Other targets include mydriasis, dry eye and myopia. The device inculdes technology to monitor administration and remind the patient if a dose is missed.

GLAUKOS
Best known for MIGS devices, Glaukos is using its stent expertise to create iDose sustained release drug delivery device. A reservoir contains highly concentrated drug which is released at a steady rate into the anterior chamber.

The initial iDose delivers travoprost using a 1.8 x 0.5 mm device inserted through a small corneal incision and

Continues on page 56: Drugs

LIV: Light Induced Visual-response
Track progression. Tailor treatment. That’s LIV-ing.

Objective clarity. Functional insights. Illuminating results.

Performing LIV tests allow you to objectively evaluate retinal health now and over time, for tailored treatment and more precise disease management.
Punctal plugs are an appealing and noninvasive sustained delivery system, but have not worked well. Until now. Mati Therapeutics has worked through more than 70 iterations to create Evolute, a straight L-shaped device that is invisible unless the eyelid is pulled down, highly tolerable, and shows up to 96 percent retention in 90-day therapy.

“When we finished phase II trials, patients didn’t want to go back on drops, reported Christopher Muller, MBA, Chief Commercial Officer. We can deliver hydrophobic or hydrophilic agents using a matrix that is specific to each drug. That lets us program an initial burst of drug, steady state release, periodic bursts or combination release, depending on the drug. That gives you more applications and more therapeutics available to you.”

In glaucoma, Evolute has tested prostaglandins, beta blockers, alpha agonists, rho kinase inhibitors and adenosine agonists over the desired therapeutic delivery period. Several agents are currently in clinical trials.

Mati is also expanding to allergy with antihistamines and mast cell stabilizers, anti-inflammatories with steroids and dexamethasone, and dry eye with immunosuppressants, an integrin antagonist and a variety of OTC demulcents, oils and emulsions.

**GRAYBUG VISION**

Graybug is developing an injectable intracameral drug depot that can deliver at least four months of sustained IOP reduction at 30 percent or more using a 30 gauge needle. Drug particles are suspended in a polymer and injected into the eye. Once injected, the polymer forms a roughly spherical depot five millimeters in diameter that releases drug at a steady rate as it absorbed. The company has completed successful clinical trials in wet AMD using sutinib.

“We have a library of more than 200 novel compounds,” said Jeffrey C. Cleland, PhD, President and Chief Executive Officer. “We are starting with single drugs and single mechanisms of action. The next step is dual agent drugs, fixed inflow plus outflow combinations. We have also developed a neuroprotective agent we are evaluating in combination with different IOP lowering drugs.”

In animal models, single drug-single MOA depots deliver 40 percent IOP lowering. Dual IOP lowering agent depots offer 50 to 60 percent IOP lowering. Depots remain outside the visual axis and are invisible to the patient.

Single drug, single MOA injections in glaucoma have shown concept works. Graybug expects to begin two large, randomized controlled trials in glaucoma in early 2019.

**OCULAR THERAPEUTIX**

Hydrogel platforms have already been approved for use in the brain, spine and eye. Ocular Therapeutics is using a proprietary hydrogel platform to deliver drugs via intracanalicular inserts, intracameral injections and intravitreal injections. An ocular sealant, ReSure, is commercially available. Dextenza, a dexamethasone punctual insert, is about to be submitted to the FDA.

In glaucoma, a three-month travoprost punctal insert is in phase 3 trials and a six-month intracameral travoprost implant is in phase 1. Non-US trials of the intracameral implant are already under way.

“In beagles, we see a 40 percent IOP reduction out to 120 days,” said Michael Goldstein, MD, MBA, Chief Medical Officer. “The technology is very programmable and we can marry the delivery to the indication and deliver drug over days, weeks or months. The depot is biodegradable and goes away about the same time drug stops eluting.”

Other programs include an intravitreal tyrosine kinase inhibitor implant and an anti-VEGF antibody implant for wet AMD, diabetic macular edema and retinal vein occlusion.

**OTERO THERAPEUTICS**

Most sustained release companies assume that eye drops are a poor drug delivery technology in glaucoma. Otero, a spinoff from research at the University of Pittsburgh, takes a more nuanced view.

“Don’t throw the baby out with the bathwater,” advised Morgan Fedorchak, PhD, President and Chief Technology Officer and Assistant Professor of Ophthalmology at the University of Pittsburgh. “We want to get rid of the problems with eye drops, low bioavailability, low adherence, side effects. And we want to keep what is of value, comfort, portability and familiarity. That’s SoliDrop, a monthly eye drop. It is administered as a fluid and transitions into a stable, solid gel depot in the fornix. You get controlled drug release for up to a month.”

SoliDrop combines a temperature responsive gel and active drug encapsulated in microspheres. Preclinical studies with brimonidine show comparable IOP reduction to twice-daily eye drops. It is relatively easy to create microspheres with drug-specific release characteristics to create unique multi-drug therapies using off the shelf agents.

The development pipeline includes glaucoma monotherapy and combination therapy as well as in vivo studies with biologics and antinfec tives plus in vitro work on anti-inflammatories.

**RETOJECT**

Topical ocular treatment wastes drug. Ten percent or less of the therapeutic dose actually reaches anterior segment tissues. Researchers at the Duke Eye Center devised a technique to access those same tissues via Schlemm’s canal and the trabecular meshwork.

“We place a ring round the eye and apply gentle compression of the venous outflow, transiently causing retrograde blood flow from the episcleral veins,” explained Molly Walsh, MD, MPH, Co-founder and Chief Executive Officer. “Any drug we then inject into the superficial episcleral veins will move into Schlemm’s canal, the trabecular meshwork and the anterior chamber. We can access these episcleral veins using a tiny 30 to 32 gauge needle. Patients don’t feel it at all.”

Injections of liposomes loaded with latanoprost plus nitric oxide in a mouse model showed clinically significant IOP reduction for about nine weeks. The liposomes can be altered to extend clinical activity longer still.

A pilot study in eight patients showed the system works in humans and is well-tolerated, Dr. Walsh reported. The company is continuing work in glaucoma and is expanding to other anterior segment therapies and is in search of nondilutive funding to move into clinical trials.

**ZORDERA**

A familiar axiom in drug development is to begin with the end in mind. That led University
of California, San Francisco researchers to explore the potential of thin film polymers for extended drug delivery. “The physiology of the eye is a major barrier to successful glaucoma treatment,” said Tejal Desai, PhD, Professor and Chair of Bioengineering and Therapeutic Sciences, University of California, San Francisco Schools of Medicine and Pharmacy. “Getting drug across the cornea is nontrivial.”

“We wanted to dial in exactly the amount of drug per day over an extended period of time. That would not only achieve compliance, but enhance efficacy, lower side effects, potentially reduce costs and make a compelling value proposition.”

The result was an engineered polymer thin film that is amenable to small molecules, antibodies and peptides and led to the founding of Zderia.

The first potential product is an intracameral film that exhibits zero order delivery up to six to 12 months, even longer with small molecules. The film can deliver monotherapy or combination therapy such as timolol plus brimonidine as well as biologics.

Dr. Desai said the company is looking for partners and additional funding to move toward commercialization.

**BIOELECTRONIC PUMP**

Sustained delivery is already a reality in diabetes and other diseases. But not yet in ocular disease. Existing pumps are too large. Mark Humayun, MD, PhD, Cornelius J. Pings Chair in Biomedical Sciences and Professor of Ophthalmology, Biomedical Engineering and Integrative Anatomical Biomedical Sciences, Keck School of Medicine at University of Southern California set out to create an implantable pump system for ocular use.

His device uses electrolysis to generate bubbles that move a diaphragm to push drug into the eye. The reservoir sits beneath the conjunctiva and can be refilled in the clinic. The cannula can go into whatever portion of the eye is most appropriate.

“The reservoir is easily refillable across the conjunctiva with a 30-gauge needle. The pump is programmable wirelessly, you can download data in the clinic and it employs surgical techniques we are all used to,” Dr. Humayun explained. He has coupled the pump with an IOP monitoring system that checks pressure every five seconds.

As long as IOP is above the desired threshold, the pump continues to delivery drug at the programmed rate and dose. Once the target IOP is reached, the pump shuts down until and unless IOP rises above target.

Dr. Desai said the company is looking for partners and additional funding to move toward commercialization.

**Aldeyra announces positive results from phase IIb dry eye clinical trial**

**ALDEYRA** Therapeutics announced positive results from its phase IIb clinical trial of topical ocular reproxalap in patients with dry eye disease.

The randomized, vehicle-controlled, parallel-group, multicenter, double-masked phase IIb clinical trial investigated 0.1% and 0.25% concentrations of reproxalap topical ocular solution versus vehicle.

Relative to patients treated with vehicle, patients treated with the 0.25% concentration of reproxalap had statistically significant and clinically relevant reductions in the Four-Symptom Ocular Dryness Score (p<0.05) and the Overall Ocular Discomfort Symptom Score (p<0.05).

Symptom improvement greater than that of vehicle was consistently observed across all measures, and activity versus vehicle was demonstrated as early as two weeks (the first assessment following initiation of therapy).

The early onset of symptomatic improvement is consistent with the phase Ila clinical trial of topical ocular reproxalap in dry eye disease, and is supportive of a differentiated product profile relative to current standard of care.

Patients treated with the 0.25% concentration of reproxalap also demonstrated reductions in ocular fluorescein staining score that were statistically superior to those of patients treated with vehicle (p<0.05).

“Based on the successful phase IIb results, we look forward to initiating a phase III program in dry eye disease in 2019 following our discussion with regulatory authorities,” said Todd C. Brady, MD, PhD, chief executive officer of Aldeyra.
Four megatrends portend ophthalmology ‘revolution’

Consolidation, private equity, risk sharing, AI sweeping the profession right now

By Laird Harrison; Reviewed by Ruth Williams, MD

No ophthalmologist can escape the impact of dramatic changes unfolding in healthcare, according to Ruth Williams, MD.

“It’s really like the industrial revolution where the changes affected everything about how people lived,” said Dr. Williams, CEO of Wheaton Eye Clinic. “The revolution in healthcare is creating chaos and affecting everything we do.”

She cited consolidation, risk sharing, private equity and artificial intelligence among the megatrends sweeping the profession.

CONSOLIDATION

“We have multiple insurance systems, multiple health systems, multiple different pharmacies, and all that is starting to change a little bit,” said Dr. Williams. In comparison to the big companies that sell most of the health insurance and pharmaceuticals, most ophthalmology practices, even large ones, are “tiny chihuahuas in the world of big dogs,” she said. “In some ways that’s been an advantage. It’s allowed us to kind of fly under the radar screen. But I do think those days are ending or at least narrowing.”

Hospitals, insurers, pharmacies, drug companies and physicians practices are all combining into larger and larger organizations, she said. Already some insurers are dominating local markets. Recently Alcon combined with Novartis, and Allergan with Actavis.

The mergers have faced some opposition. Dr. Williams pointed out that the U.S. Department of Justice blocked the merger of Anthem and Cigna and of Aetna and Humana, and that Walgreens had backed off a bid to acquire Rite Aid that was being scrutinized by the U.S. Federal Trade Commission.

But she added that CVS is attempting to acquire Aetna. “If that goes through, it will be an innovation and disruption of the market,” she said. CVS already operates pharmacies and walk-in clinics “so CVS will now be the insurance company, the provider, and the pharmacy all in one company.”

The merger of healthcare systems is affecting ophthalmologists, partly through Medicare Advantage, which is growing rapidly, Dr. Williams said. Hospitals are pitching visitors on their Medicare Advantage programs. “They sign up in the lobby of the hospital and they become patients of the health system. Then they can only go to the doctors who are contracted with that health system. So if you’re in, great, if you’re out, you’ve just lost access to one of your long-term patients.”

Health systems have an advantage in starting these insurance products because they can often enroll thousands of their own employees, Dr. Williams said. The number of ophthalmologists in solo practice has declined over the past 2 years, she added, reaching about 26% in the most recent survey.

RISK SHARING

Ophthalmologists who still run their own businesses are having to take on more risk, Dr. Williams said. The practice is responsible for collecting deductibles and copayments. These are rising, reaching thousands of dollars in some cases.

Post-payment audits also shift risk to physicians, she said. “You can do the whole procedure and after the fact, the insurance company can come back and say, ‘Oh, no, no, no. That wasn’t appropriate.’ And you have to pay them back after you’ve done everything.”

Risk sharing also takes the form of buy-and-bill, where physicians purchase and administer drugs, then collect payments afterward.

‘It’s really like the industrial revolution where the changes affected everything about how people lived. The revolution in healthcare is creating chaos and affecting everything we do.’ — Ruth Williams, MD
“Those of you have aflibercept [Eylea] in your practices have experience with it,” said Dr. Williams. “But buy-and-bill is coming to all of us. Talk to your retina specialists and find out how they do things.”

But risk sharing isn’t all bad, Dr. Williams said. Risk-based contracting offers some upside potential for practices “if you know what you’re doing.”

These contracts can range all the way from capitation, in which providers are paid a flat rate to care for a population, to bundled payments where they are paid by an “episode of care,” or contracts that simply offer bonuses and penalties based on outcomes and patient satisfaction.

PRIVILEG EQUITY

While it doesn’t have the potential to transform practices in the same way as consolidation, private equity firms’ interest in medical practices remains a hot topic, said Dr. Williams. “I think we’re all excited about it, and interested, and curious.”

Some of these firms are looking for robust ophthalmology practices they can buy. While they may take different approaches, many will try to grow the practices, then sell them in 3 to 5 years, said Dr. Williams. Seeking investors can be important to practices when they have succession issues or need capital, she said.

She cited the example of DuPage Medical Group, a larger physician-owned practice in Illinois that has grown rapidly in recent years. It recently received a $1.45 billion investment from Ares Management.

“They have a lot of leverage,” said Dr. Williams. “They can move around which hospital they send their patients to. So they really do put a little pressure on the big hospitals.”

Armed with this cash, some large practices are shopping for smaller practices to continue their expansion, said Dr. Williams.

“It may be a bigger fish that private equity has infused cash in that might be wanting to buy you.”

ARTIFICIAL INTELLIGENCE

Many advocates of artificial intelligence (AI) believe it will transform healthcare, and the American Academy of Ophthalmology has taken an interest in the topic, said Dr. Williams.

As an example of the potential, she pointed out that currently it is difficult to measure the progression of glaucoma in 1 or 2 visual field tests.

“None of us are mean enough to bring our patients in every month for 5 visual fields,” she said.

But Filipe Madeiros, MD, PhD, of Duke University is developing a method by which virtual reality goggles could allow patients to do the visual field tests at home. “AI would help us figure out who the fast progressors are.”

She also cited the work of Joshua Stein, MD, MS, at the University of Michigan, who has helped developed statistical models to project glaucoma projection.

“He’s bringing data together from multiple different places, and we can figure out which patients need a field every 4 years and which one needs 3 in a row in the next month,” Dr. Williams said.

How can ophthalmologists navigate through this shifting landscape?

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Three time management skills to achieve financial success

Rework old communication habits by taking a leap of faith out of your comfort zone

By Donna Suter

CONFESSION NUMBER ONE: I am the queen of making promises. “I'll never do that again!” “I'll never say that again…” “I am going to change beginning right now.”

Many such promises are forgotten within hours. At the heart of most of us is the desire of change. Confession number two: Sometimes, I feel like a loser.

However, once I mentally review the facts and hang out with people who value my worth, I’m able to snap back. I need to remind myself that there is a bigger picture, and discouragement is only a temporary setback.

Often, false promises and self-doubt can rear their ugly heads when it comes to practice management.

Being successful as a small business owner in today’s healthcare climate takes hard work. The small things that hinder our progress add up, yet we tend to ignore these things: personal use of time, personnel, and money management. These three things will make or break most practices.

PERSONAL TIME MANAGEMENT

Let’s begin with personal time management. When I was getting my master’s, a professor began the course by making us track, then graph, the use of our hours for five days.

Can you imagine what a PITA it was to set a stop watch and record what I’d done for the last hour, for every waking hour, from Monday through Friday? The professor ensured compliance by tying a full 1/3 of our grade to this assignment.

Taking the raw data and charting it revealed that, while I couldn’t fabricate more hours in a day, I could eliminate or reduce certain activities and make time to study and make an A in my classes. (Why I needed to end up with a 3.96 GPA in my master’s studies, I still don’t know.)

You invested much more time and money into opening your practice than I did getting a master’s. Doesn’t the dream of being self-employed deserve your best? Given your intellect and history of determination, you can be successful. Your best ideas can move from soon-forgotten to agents of change with enough time.

So, what’s holding you back? Do you have a list of things you want to change? Do you think about the concrete steps needed to achieve the desired change?

TAKE-HOME

› Stop making mental promises your goals. Instead, focus on tangible time and money management skills to improve productivity, and practice these new habits with a trusted support system.

PERSONNEL

Don’t blame practice management frustrations on the work ethic of differing generations. Just like rock and roll didn’t destroy my moral fiber, hiring millennials to work in your office won’t cause your practice to go bankrupt.

In an ideal world we would all understand each other and accept everyone’s unique approach to life—recognizing the positive intent behind behaviors. But let’s face it, when it comes to communication we all get triggered by something.

Books are written on how communication blunders cost businesses. By failing to recognize and adjust communication habits that are not serving you well, you may be jeopardizing the tenure of your peak performers and enabling your less-than-loved employees to continue down a path of disrespect. Unfortunately, this path often leads to embezzlement of practice time, resources and eventually money.

Communication habits causing you the most problems now are the very ones that led to your greatest successes in the past. The trouble comes when these are the only communication habits that you use.

If you are wondering why your coaching sessions aren’t motivating employees to change, it may be how you are packaging the message—meaning, word patterns and body language.

What might motive you to change how you speak to others? Carefully consider the consequences of not changing—refusing to evolve and grow, staying stuck in the loop created by today’s healthcare delivery system and your own sense of a “right” and “wrong” way of doing things.

Take time to weigh the benefits of choosing to access a greater range of more resourceful, productive behaviors that affords you a higher quality communication and generate a positive response from others.

Read books about communication styles; practice your emerging skills on family members and strangers; hire a communication coach.

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It takes time to develop new habits. (This is where that group of people I mentioned in paragraph two—those who value your worth—come into play. Share a change goal and give them permission to hold you accountable.)

Reading will help you identify your practice’s most important problems, add them to your change list, apply durable fixtures, and enjoy the professional life you deserve.

MONEY MANAGEMENT
Have you ever realized you’ve been completely unaware of something you should be thinking about? Money management and budgets based on projections are two of those fundamental assumptions of successful practice management that a successful small business owner has to get her or his arms around. When you do, you begin to realize that it affects your practice in so many ways.

Hacking your financial management system and re-working it allows you to function at a higher profit level. Basic accounting has a tendency to focus on the what: what areas of the practice are spending the most money, what are fixed versus variable expenses, etc.

Until recently, healthcare has completely ignored consumer preference and a marketing budget was just as optional as money set aside to build teamwork among employees.

Become a student of business management. A little light reading will help you to identify your practice’s most important problems, add them to your change list, apply durable fixes, and enjoy the professional life you deserve. (I just quoted a tagline from the front of a book written by John B. Pinto.)

I have no financial interest in his books and only a professional, colleague relationship with Pinto. However, the reason I have never written a book about practice turnaround is because every tactic I have used for 25 years is described in detail in this little gem of a book.

Are you thinking about the changing seasons and changing? Perhaps picking back up that dearly held dream of running a successful practice while maintaining balance? Your feelings motivate you more than facts. Just like you don’t tell someone with a bad health habit their lifestyle is going to kill them, challenge yourself to use truisms from practicing medicine to achieve professional success.

REVIEW THE FACTS AND DISCOVER YOUR TRUTH
Acknowledge that if you loved and admired yourself as much as your core group of family and friends do, you’d never keep those habits that are not working to build the practice of your dreams. The truth is that your perception of yourself and your ability to change may be limited by your fear of failure.

Truthfully, my mental promises are not my goals and I don’t run my business nor professional career without thoughtful planning and attention to goals.

It’s amazing how gifted professionals underestimate what can be accomplished in a year. Figure out what you love that happens to be working, focus on doing that regularly; and, with the help of your support group, prioritize and devote an hour a day to one thing on your change list.

FINANCIAL BALANCE
(Continued from page 60)

EMA will begin review of the MAA for netarsudil, currently marketed as Rhopressa in the US

AERIE PHARMACEUTICALS announced that the EMA has accepted for review the MAA for netarsudil ophthalmic solution 0.02% (Rhokiinsa). The agent is currently marketed as Rhopressa in the United States and is indicated for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

An opinion from the EMA’s Committee for Medicinal Products for Human Use on the MAA for Rhokiinsa is expected in the second half of 2019, according to the company.

“We are delighted that the European regulatory authorities have accepted our Rhokiinsa filing for review. If Rhokiinsa is approved, we plan to submit an MAA for Roclatan shortly thereafter,” said Vicente Anido, Jr., PhD, chairman and chief executive officer at Aerie.

“Our Mercury 3 phase III trial for Roclatan, Aerie’s fixed-dose combination of Rhopressa and latanoprost, is ongoing in several European countries, and we continue to expand our presence in Europe with nearly 60 employees on board,” Dr. Anido said.

In addition to a manufacturing facility in Ireland, the company is building its clinical, medical affairs and commercial teams in the European region.

Additionally, the company was well-represented at the recent 36th Congress of the European Society of Cataract and Refractive Surgeons in Vienna, including an active booth and our presentations and panel participation at the Ophthalmology Futures Forums, he noted.

Dr. Anido continued, “Separately, our plans remain on schedule for the initiation of our phase II clinical trial for Rhopressa in Japan in near future, including the opening of an Aerie office in Tokyo.”

OCTOBER 1, 2018: Ophthalmology Times

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OCTOBER 1, 2018: Ophthalmology Times

62 (practice management)
What is Inherited Retinal Disease (IRD)?

IRD is a class of single-gene disorders that represent the major cause of familial blindness in the Western world, and until recently, have been untreatable.

This website hosts a series of CME/CE-accredited educational activities that present updated guidelines for diagnosis, referral patterns, and treatment, all of which have changed dramatically in the past year. It is also where busy clinicians can find valuable resources, which will include video interviews from the 2018 AAO Conference with the leading subject matter experts on gene therapy for IRD.

These educational activities were planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) by the Institute for Continuing Healthcare Education. The Institute for Continuing Healthcare Education is accredited by the ACCME to provide continuing medical education for physicians.

The Institute for Continuing Healthcare Education designates these educational activities for a maximum of 4.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in these activities.

These activities are supported by an unrestricted educational grant from Spark Therapeutics.
The vision needs and goals of the contemporary population of cataract surgery patients differ from past generations. Many now are continuing to work later in life, staying more active, and are using computers, smartphones, and other digital technology. As a consequence, they are relying more on intermediate and distance vision and placing greater value on reduced spectacle dependence.

Today, cataract surgeons are able to address these needs and goals better than before thanks to advances in intraocular lens (IOL) technology. Selection of appropriate patients for these implants and setting proper expectations about the results, however, are still critical for achieving successful outcomes and satisfied patients.

Choosing the right candidate
Not all cataract surgery patients are interested in or are suitable candidates for a presbyopia-correcting IOL. To gather information about a patient’s vision needs and goals, willingness to tolerate the compromises associated with presbyopia-correcting IOLs, and personality, we use a modification of the Dell questionnaire and ask them about current and future plans for work, hobbies, and recreational pursuits. A healthy ocular surface is also critical for good outcomes with a presbyopia-correcting IOL, because it affects both the veracity of preoperative biometry measurements and the quality of postoperative vision. Therefore, ocular surface disease must be identified preoperatively, and those patients whose ocular surface cannot be optimized may need to be excluded. In addition, good candidates for presbyopia-correcting IOLs should have no significant macular, optic nerve, or zonular issues.

Personality is important as well, but although easygoing patients tend to do better with presbyopia-correcting IOLs, I do not routinely rule out anyone who seems highly demanding. Success is possible with such patients if they are properly informed about their potential outcomes so that they have realistic expectations. All patients considering a presbyopia-correcting IOL need to understand that with currently available technology, they will have to accept some compromises to get the advantage of a broader range of vision. Weighing the potential downsides and benefits, however, I believe the TECNIS Symfony® extended-depth-of-focus IOLs stand out from the competition.

TECNIS Symfony® IOLs
The TECNIS Symfony® and TECNIS Symfony® Toric IOLs are constructed of time-tested acrylic material that is not associated with glistening. The optic combines the benefits of spherical aberration compensation with chromatic aberration correction to provide excellent quality of vision with a low incidence of nighttime visual symptoms. The proprietary diffractive echelette design of the TECNIS Symfony® IOL creates an extended depth of focus, resulting in a smooth defocus curve that is free of real dips such as are seen in a multifocal IOL defocus curve (Figure 1). For patients, this translates into a continuous range of vision. Visual acuity outcomes show that the TECNIS Symfony® IOLs provide excellent uncorrected vision at intermediate and far distances and functional uncorrected vision at near. Nevertheless, I tell all patients that there is a good chance they will have to wear glasses for reading small print. Depending on what materials they are reading, the lighting conditions, and for how long, some of my TECNIS Symfony® IOL patients tell me they have no need for reading glasses. These individuals are especially thrilled because their expectations were exceeded.

Another benefit of the wide defocus curve of the TECNIS Symfony® IOL is that it allows for a larger landing spot when it comes to hitting the refractive target. Vision outcomes are therefore less sensitive to residual refractive error. That being said, I believe that the TECNIS Symfony® IOL performs best when I hit my refractive target. With TECNIS Symfony® Toric, I can offer presbyopia-correcting IOL technology to a larger pool of patients. Furthermore, with many of the mentioned features in mind and after providing thorough patient counseling and informed consent, I now feel comfortable discussing a TECNIS Symfony® IOL in certain patients for whom I would not have previously considered implanting a multifocal IOL.

My patient conversation
Some patients needing cataract surgery are unaware of the opportunity to reduce their dependence on glasses postoperatively. Another segment of patients come in for their preoperative evaluation having done some research and gained familiarity with the various IOL options. Other patients present requesting a specific IOL because they know someone who is happy with that lens.

Even if a surgeon does not offer a particular type of lens or does not feel comfortable recommending a certain type to
an individual, I believe that patients should be told about all available technologies. With this approach, patients become active participants in the decision and understand it is being tailored to their specific situation. The chance is low that a patient will decide to find a different surgeon because they are told that a particular presbyopia-correcting IOL is not offered or is not appropriate for them.

My general approach to educating patients about IOL options is to explain the different types of lenses by introducing them in broad categories. I tell patients that my job and goal as a surgeon is to pick the right lens for them, taking into account their lifestyle, expectations, the current state of their eye, and anticipated changes in their ocular health.

No perfect algorithm exists for selecting patients who will be happy and successful with the TECNIS Symfony® IOL or with any other presbyopia-correcting lens. I am very frank about this with patients, explaining that there is no perfect IOL on the market. With every IOL, there is some compromise. Therefore, I educate patients that we need to take many factors into account to try to determine what IOL will make them most happy. Often, I use shoe fitting as an analogy to help them better understand. I say that their foot may actually be a size 9.75, but given what is available in the market, we need to choose whether they will be most comfortable wearing a size 9.5 or a size 10, recognizing the tradeoffs of each. Then, I add in the consideration of shoe width as an analogy for choosing between a nontoric lens and a toric lens.

The Vision Simulator from Johnson & Johnson Vision is a useful tool for helping patients understand the effects of presbyopia and astigmatism on vision along with the profiles of the different IOL options (Figure 2). To help patients grasp the functional performance differences among monofocal, multifocal, and extended-depth-of-focus IOLs, I also like to mimic defocus curves with hand motions so that they can perceive how the lenses function differently depending on where they are focusing.

I use the Vision Simulator to establish expectations about nighttime vision symptoms. When recommending a TECNIS Symfony® IOL to patients, I show the picture for the TECNIS® Multifocal IOL. Although the incidence of nighttime vision symptoms was low in the TECNIS Symfony® IOL clinical trials, I would rather that patients decide if they can accept these problems by seeing a worst-case scenario than be unhappy postoperatively because they had a different expectation. I also explain that if nighttime symptoms occur, these typically diminish with time.

Conclusion

Presbyopia-correcting IOLs give surgeons the opportunity to meet the needs of a growing number of patients in today’s cataract surgery population. In my experience, the TECNIS Symfony® IOLs allow me to achieve a high level of patient satisfaction. My recommendation to colleagues who are not yet using the TECNIS Symfony® IOLs is to begin by using stringent patient selection criteria. Additionally, always counsel patients thoroughly about the benefits and potential risks and use this technology for a particular individual only if you think it is the most appropriate lens for the patient, remembering that each patient is unique and no one IOL fits all. Having followed these tenets myself, both my patients and I have been very happy.

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5. DOP2015CT0020_Symmetry_MT versus competition.

INDICATIONS and IMPORTANT SAFETY INFORMATION for TECNIS Symfony® IOLs

TECNIS Symfony® IOLs are intended for capsular bag placement only. The Model Série ZXT IOLs are intended for capsular bag placement only. The TECNIS Symfony® IOLs are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients.

SERIOUS ADVERSE EVENTS

Physicians considering lens implantation under any of the conditions described in the Directions for Use should weigh the potential risk/benefit ratio prior to implanting a lens. Some visual effects associated with multifocal IOLs may be expected because of the superposition of focused and unfocused images. These may include a perception of halos, glare, reduced contrast, and glare under nighttime conditions. It is expected that, in a small percentage of patients, the observation of such phenomena will be annoying and may be perceived as a handicap, particularly in low illumination conditions. On rare occasions, these visual effects may be so significant that the patient will request removal of the multifocal IOL. Contrast sensitivity is reduced with a multifocal lens compared to a monofocal lens. Therefore, patients with multifocal lenses should exercise caution when driving at night or in poor visibility conditions.

IOLs are indicated for capsular bag placement only. In clinical trials of the TECNIS Multifocal lenses was surgical re-intervention, most of which were non-lens-related. Lens-related re-interventions occurred at a rate of 0.6% to 1.5%. Other surgical re-interventions included lens exchanges (for incorrect IOL power), retinal repair, ruptured globe repairs, macular hole repairs, or retained lens material.

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.
Consider these tips to maximize your time at professional medical events

By Pamela Tabar

MEDICAL SYMPOSIA, industry conferences, and professional development workshops are great opportunities to network with peers, hear innovative ideas, and recharge professional passions. They also can be cognitively overwhelming.

Sure, you’ll leave inspired to make improvements in your practice. But it can be difficult to hold on to those aspirations once you get back to the daily grind.

We asked physician practice “conference junkies” how they make the most of their time at conferences, including tips on how to keep those best practices top of mind and even put them into action.

BEFORE THE CONFERENCE
Long before you board the plane, decide what you and your practice teams hope to learn from the specific event, suggested Owen Dahl, a practice management consultant in The Woodlands, TX, and a frequent speaker at physician practice management conferences.

“Planning needs to start before the conference, both on what the big organizational needs are and the goals of the individual,” he said. “Go with the expectation of identifying two or three major things that can be brought back.”

For first-time conference attendees, the conference experience can induce information overload, said Krisemily McCrory, MD, FAAFP, a family medicine practitioner in Schenectady, NY.

“Look at the schedule, and plan your days ahead of time,” she urged. You can’t possibly attend everything, so identify the sessions that relate specifically to your practice interests or may offer ideas on how to improve your processes.”

Study the conference agenda and identify a backup session in case your primary intended session is overbooked, canceled, or doesn’t offer the information you expected. But don’t feel pressured to marathon from one session to the next. In most cases, it’s counterproductive to attend too many sessions in a day.

“You can end up with a fair degree of cognitive overload and, paradoxically, retain very little,” said Saroj Misra, DO, FACOFP, chief of family medicine at St. John Macomb-Oakland Hospital in Warren, MI, and a veteran of the conference circuit.

DURING THE CONFERENCE
It’s your conference dollar, so maximize your attendance by focusing on your educational goals and taking the opportunity to ask questions of the speakers, Dr. McCrory said.

“For each session you attend, write down one or two action items you can take home. Try not to change your entire practice based on a single session, but use the pearls to make smaller, more manageable changes. See if the presenters are willing to share contact information—often they will be available to answer questions via email after you have had time to digest the material.”

Is a session’s content not what you’d hoped it would be? It’s not a sin to get up and switch to another session, so maximize your time by moving on to your Plan B session. You’ll be tired at the end of each day, but don’t be tempted to skip networking opportunities offered in the evenings.

It’s a great way to exchange ideas with other attendees in an informal setting (be sure to keep your name tag on), and there are usually appetizers to snack on while you mingle. Nearly every conference has a social media presence, so harvest those social media tools, Dr. McCrory added.

“Don’t underestimate the connecting power of social media. If you don’t have a Twitter account, consider getting one and using it for the conference. You will find other attendees you can connect with virtually and in real life, and you’ll be informed of impromptu or informal gatherings that might not be on the schedule.”

It doesn’t hurt to make sure your LinkedIn profile is up-to-date, as some people like to send out invitations while talking to you on your phone. And even in this digital day and age, handing out old-fashioned business cards remains a great way to connect later.

AFTER THE CONFERENCE
Once you unpack your suitcase, it’s easy for the conference inspirations to fade. Make a point of reviewing your take-home lessons or change-nuggets and sharing them with others in your practice. Most presenters offer downloadable materials from their presentations, but not all conferences keep those resources available forever—so be sure to download what you wish to keep within a week or so after the conference.

“Translating what you learned into what you do takes practice,” Misra notes. “Small, focused changes are easier. Try to pick one or two things you wish to change about the way you practice. Next, try to engage others in your practice. It may be a medical care change or a workflow change. Remember, you have to be able to explain succinctly what you think should be changed and why. If you have a weekly staff meeting or practice meeting, this might be an excellent place to introduce such ideas.”

Instituting changes in your practice means laying out a goals plan and considering all departments that may be affected. “Set a goal of achievement, such as three to six months to realize the benefits of a change,” Dahl suggests. “Small, incremental steps rather than a Big Bang approach may be the best way to go. The key factor is what makes sense and then what is possible to achieve.”

Editor’s Note: This article originally appeared in sister publication Physicians Practice.
How to extract motivating benefits from negative patient reviews

Be proactive in enhancing your social media presence in positive ways

By Rebekah Bernard, MD

I RECENTLY READ Gloria Kim, MD’s excellent essay, “How Yelp made me a better doctor (https://bit.ly/2OSDKJM),” a runner-up in the Medical Economics 2018 Physician Writing Contest. Dr. Kim, an OB/GYN, was devastated when a patient wrote a scathing review of her on Yelp. Dr. Kim had provided thorough, caring service for a patient and had certainly done nothing to warrant the fury that emanated from the review, “skewering everything about me and my office with vehement gusto.”

Dr. Kim spent a great deal of time thinking about this negative review. She perused on the review for months. The review devastated Dr. Kim. A conscientious and caring physician, she writes in her essay that “I really wanted [my patients] to like me.”

As I read this essay, my heart ached for Dr. Kim, and for every physician who faces the dilemma of “asymmetrical rewards.” In other words, all the hard work and effort put into 99% of your day can completely fade away in response to one single negative response or complaint.

In the case of Dr. Kim, the good work that she did “spending sometimes over an hour with a distressed patient...telling me of her disintegrating marriage” or “another patient [telling me] of her teenage son’s horrific and tragic death” was meaningless compared to one patient who was dissatisfied with her, for no obvious reason.

While Dr. Kim was able to make the best of her situation, using the negative review as an opportunity to make improvements in her workflow, other physicians may find themselves feeling burned out when they face angry patient reviews.

But what if I told you that the occasional negative patient complaint online could actually turn out to be a good thing for your reputation?

BAD REVIEWS BRING OUT YOUR CHAMPIONS

The other positive thing that can happen when we get a negative review is that the occasional detractor can bring out our champions. Most of the time people who really like us don’t take the time to write us reviews. But when patients who like their doctor see a vicious review of a doctor that they care about, then look out! Patients will often rush to that doctor’s defense, and you will then see a string of positive reviews that quickly neutralize a negative review.

PAGES

Although this may happen organically, we can always improve our online reviews by asking our patients to write reviews of our practice. There is nothing wrong with this. The more positive reviews that you have online, the less likely that a negative review will be noticed.

TAKE CONTROL

Another way to negate unwanted comments on review sites is to take control of your social media and web presence. Marjorie Stiegler, MD, an expert on social media for physicians and the author of “The Social Prescription: How Savvy Doctors can Leverage Digital Platforms for Professional Success” points out that the more web presence you have, the more likely it is that when someone searches for your name or practice, your own sites that you control show up ahead of doctor rating review sites.

Start by making a Google page for yourself and for your business, as well as a Facebook page. You can add a Twitter account or Instagram if you feel ambitious. Create a website using an online service that makes it easy to do yourself or hire a professional website developer to help you. Many online websites even offer free SEO (search engine optimization) services that allow search engines like Google to find your website when people are searching for keywords that you have linked to your site (“family physician” or “general surgeon,” for example).

Finally, remember that although negative reviews are inevitable and are unlikely to actually hurt your practice, they can cause emotional distress. When we get a negative review or an angry letter from a patient, we need to acknowledge our feelings. We all want to be liked, and we work hard for our patients.

Usually patient complaints are related to some type of misunderstanding or confusion, but they are rarely something that the patients are willing to work on if they are at the point of firing off angry letters or reviews. As physicians, we must reconcile ourselves to this—it is impossible to please everyone, no matter how hard we try. Perfectionism is an impossible ideal, and if we expect perfection from ourselves, we will inevitably fail. Seeing ourselves as failures, or inadequate as physicians, is one of the major hallmarks of burnout.

All the more reason that psychology can help! Dr. Kim suggests in her essay that residency training should include psychology and indeed, psychology is something that can truly benefit all physicians. We can also use psychology to help our patients more effectively, and hopefully mitigate their urge to write those negative reviews that we hate so much.

Editor’s Note: This article originally appeared in sister publication Medical Economics.

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INDICATIONS AND USAGE

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSEAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. TRAVATAN Z® (travoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

TRAVATAN Z®: Solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Pigmentation

TRAVATAN® (travoprost ophthalmic solution) has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periocular tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periocular tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation.

Intraocular Inflammation

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

Macular Edema

TRAVATAN® Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis

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

Use with Contact Lenses

Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

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. The most common adverse reaction observed in controlled clinical studies with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN® (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN® or TRAVATAN Z®: Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

In postmarketing use with prostaglandin analogs, periocular and lid changes including deepening of the eyelid sulcus have been observed.

PATIENT COUNSELING INFORMATION

Potential for Pigmentation

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z® (travoprost ophthalmic solution) 0.004%.

Potential for Eyelash Changes

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z® Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container

Patients should be instructed to avoid allowing the tip of the dispensing container to come in contact with the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

NEW CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 160 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 62 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat 5-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day (250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)). At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

PREGNANCY

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use

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

Hepatic and Renal Impairment

TRAVATAN ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

TRAVATAN Z® Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z® Solution is administered to a nursing woman.

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When to Seek Physician Advice

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z® Solution.

Use with Contact Lenses

Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Rx Only

U.S. Patent Nos. 5,631,287; 5,889,052, 6,011,062; 6,235,781; 6,503,497; and 6,849,253
Intraocular Inflammation of lashes. Eyelash changes are usually reversible upon discontinuation of treatment. Hair in the treated eye. These changes include increased length, thickness, and number.

Pigmentation

Warnings and Precautions

IMPORTANT SAFETY INFORMATION

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

INDICATIONS AND USAGE

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dosage is one drop in the affected eye(s) once daily in the evening. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP lowering effect.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

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

Use with Contact Lenses—Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Adverse Reactions

The most common adverse reaction observed in controlled clinical trials with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN Z® Solution was ocular hyperemia, which was reported in 30% to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5% to 10% in these clinical trials included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus.

Additional adverse reactions have been identified during post approval use of TRAVATAN® or TRAVATAN Z® in clinical practice. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to TRAVATAN® or TRAVATAN Z®, or a combination of these factors, include: arrhythmia, vomiting, epistaxis, tachycardia, and insomnia. In postmarketing use with prostaglandin analogs, peribulbar and lid changes including deepening of the eyelid sulcus have been observed.

Use in Specific Populations

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

For additional information on TRAVATAN Z® Solution, please refer to the Brief Summary of Prescribing Information on the following page.

*Study Design: Double-masked, randomized, parallel-group, multicenter noninferiority comparison of the efficacy and safety of travoprost 0.004% preserved with benzalkonium chloride (BAK) and TRAVATAN Z® Solution after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension. Mean baseline IOPs were 27.0 mm Hg (n=322), 25.5 mm Hg (n=322), and 24.8 mm Hg (n=322) at 8 AM, 10 AM, and 4 PM for TRAVATAN Z® Solution. At the end of month 3, the TRAVATAN Z® Solution group had mean IOPs (95% CI) of: 18.7 mm Hg (-0.4, 0.5), 17.7 mm Hg (-0.4, 0.6), and 17.4 mm Hg (-0.2, 0.8) at 8 AM, 10 AM, and 4 PM, respectively. Statistically equivalent reductions in IOP (95% CI about the treatment differences) of 18.7 mm Hg (-0.4, 0.5), 17.7 mm Hg (-0.4, 0.6), and 17.4 mm Hg (-0.2, 0.8) were demonstrated between the treatments at all study visits during the 3 months of treatment.
