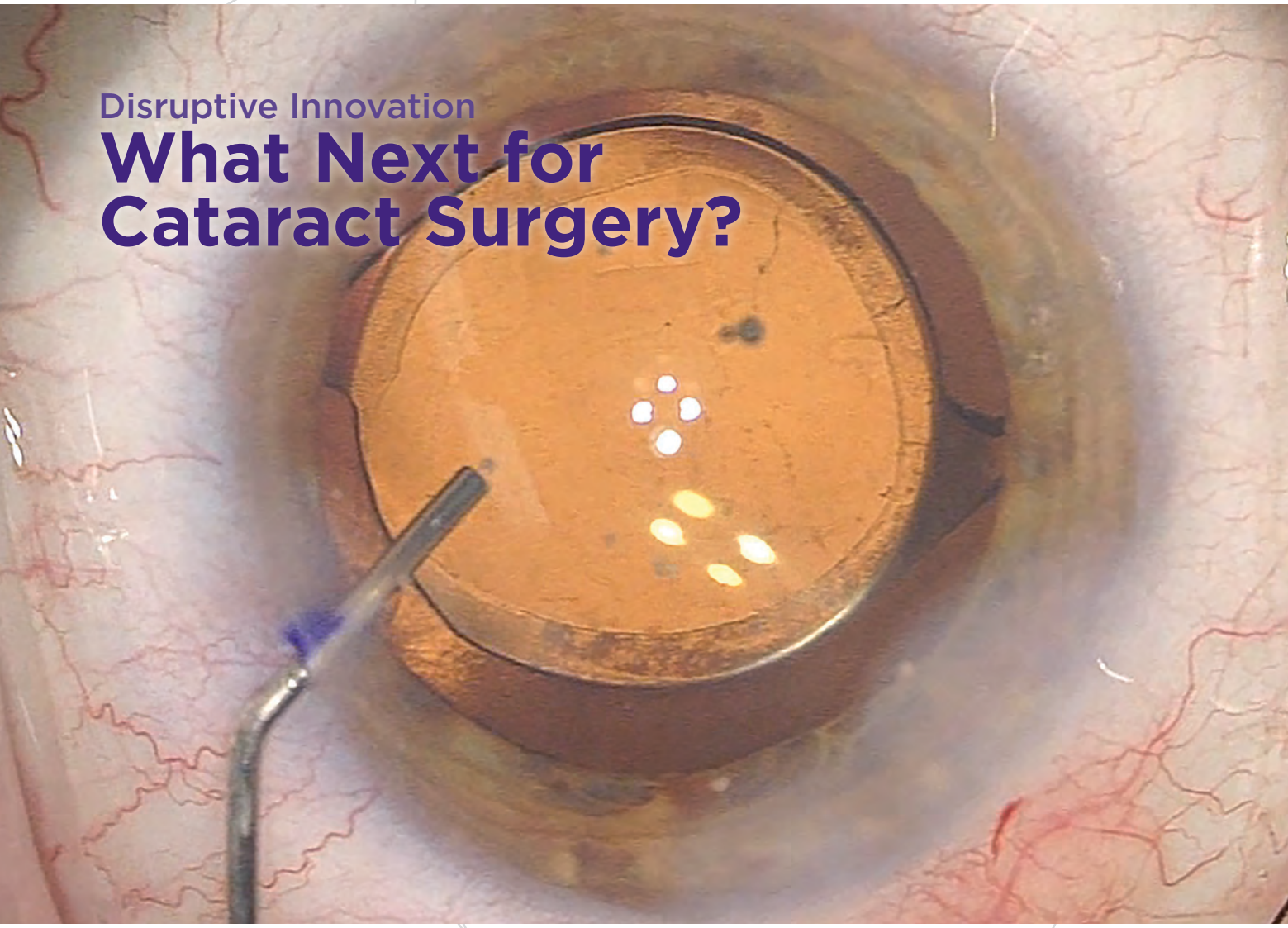
AMERICAN ACADEMY OF OPHTHALMOLOGY®

EyeNet®

SEPTEMBER 2018



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Pros and Cons of Intraoperative OCT

Pearls

Giant Retinal Tear

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- Omeros continues to support access to OMIDRIA through the OMIDRIAssure® Patient Assistance Program

INDICATIONS AND USAGE

OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

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.

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The most commonly reported adverse reactions at ≥2% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Please see the Full Prescribing Information for OMIDRIA at www.omidria.com/prescribinginformation.

You are encouraged to report Suspected Adverse Reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017.

Visit www.omidria.com

Omeros does not guarantee reimbursement by any third-party payer. To be eligible for the "Equal Access" Patient Assistance Program, patients must be enrolled in OMIDRIAssure prior to surgery. For any patient for whom your facility received a free vial through the "Equal Access" Patient Assistance Program, the patient's insurance carrier(s) should not be billed for OMIDRIA. OMIDRIAssure program services are subject to change without notice.

OMIDRIA®
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1% / 0.3%

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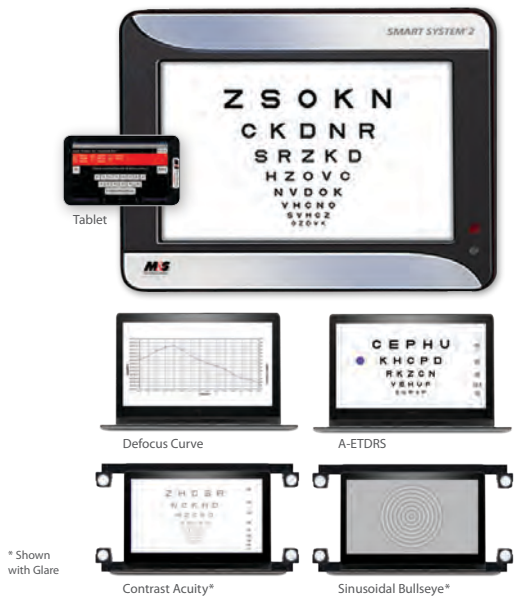

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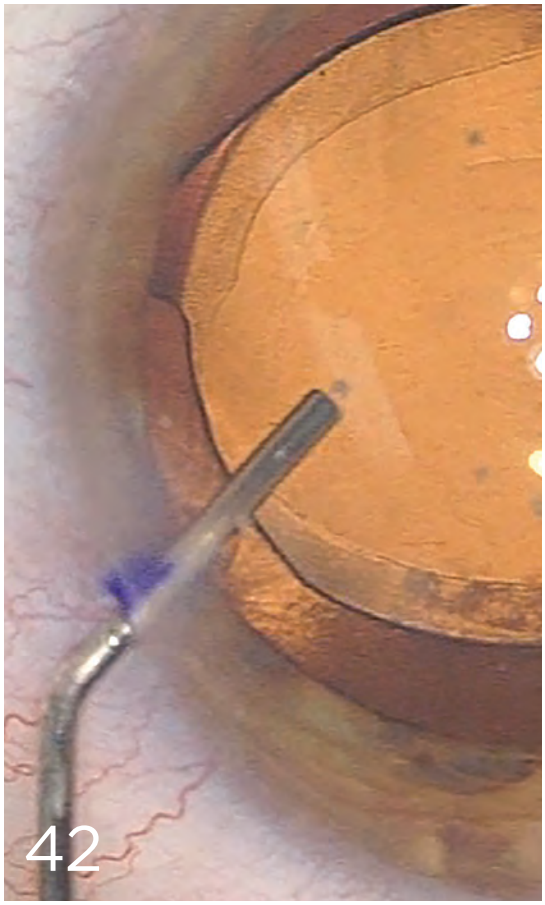

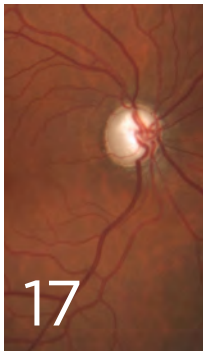

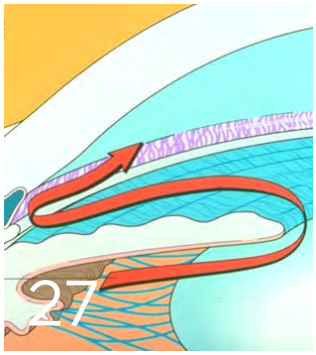

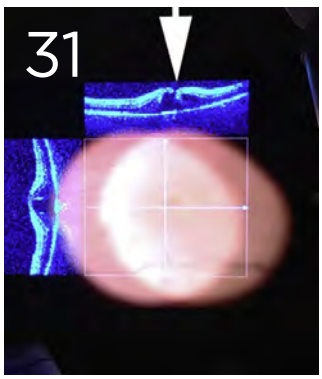

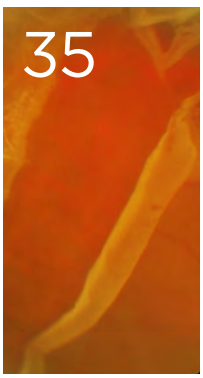

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SEPTEMBER 2018
VOLUME 22 • NUMBER 9

AMERICAN ACADEMY OF OPHTHALMOLOGY®

EyeNet*® *Magazine (ISSN 1097-2986) is published monthly by the American Academy of Ophthalmology, 655 Beach St., San Francisco, CA 94109-1336, as a membership service. Subscription is included in U.S. members' annual dues. International Member, IMIT, $135 per year. Nonmember in U.S., $150 per year. Nonmember outside U.S., $210 per year. Periodicals Postage Paid at San Francisco, CA, and at additional mailing offices. POSTMASTER: Send address changes to *EyeNet*, P.O. Box 7424, San Francisco, CA 94120-7424.

COVER PHOTOGRAPHY

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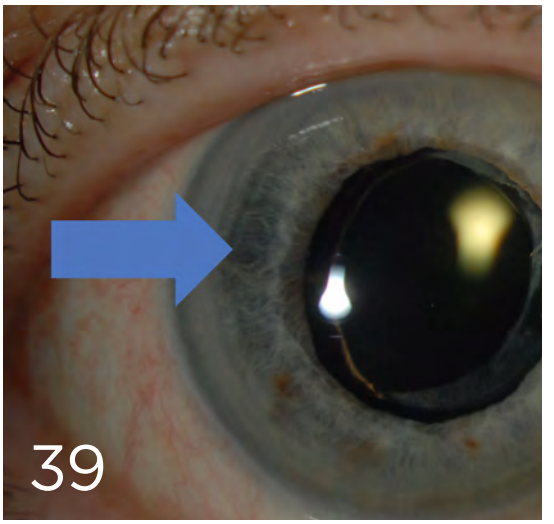

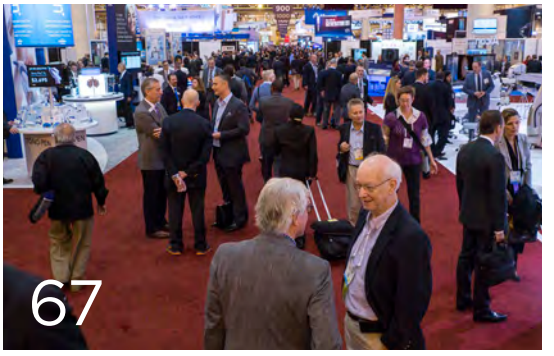

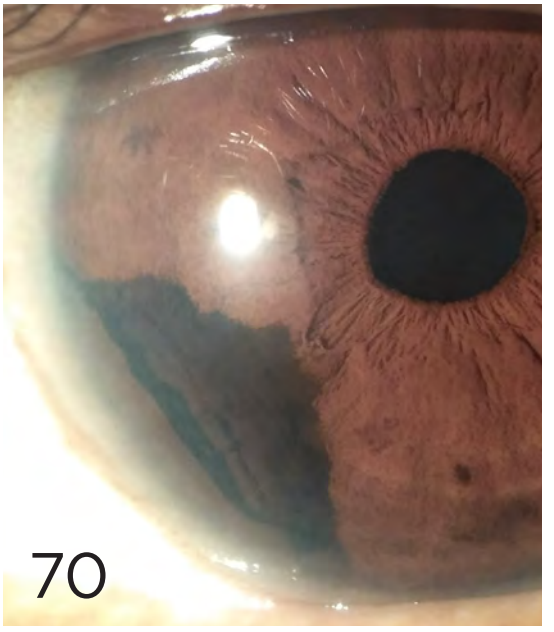

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› Provides IOP reduction of up to 5 mmHg[1]

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The most common ocular AE observed in controlled studies with Rhopressa® was conjunctival hyperemia (reported in 53% of patients)[1]

AE, adverse event; IOP, intraocular pressure; ROCK, rho-associated protein kinase.

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INDICATION

RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure 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.

IMPORTANT SAFETY INFORMATION

Dosage and Administration: Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA® is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

Warnings and Precautions:

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.

Adverse Reactions: The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA® dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients. The corneal verticillata seen in RHOPRESSA®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

Please see the adjacent page for Brief Summary of Safety Information. For full Prescribing Information, please visit Rhopressa.com.

REFERENCES: 1. Rhopressa [prescribing information]. Irvine, CA: Aerie Pharmaceuticals, Inc; 2017. **2.** Serle JB, Katz LJ, McLaurin E, et al; and ROCKET-1 and ROCKET-2 Study Groups. Two phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure. *Am J Ophthalmol*. 2017;S0002-9394(17)30513-5. **3.** US Department of Health and Human Services, Food and Drug Administration Dermatologic and Ophthalmic Drugs Advisory Committee briefing document: NDA 208254. Published October 13, 2017. **4.** Bansal R, Tsai J. Compliance/adherence to glaucoma medications—a challenge. *J Curr Glaucoma Pract*. 2007;1(2):22-25.

aerie Pharmaceuticals, Inc.

RHOPRESSA® (netarsudil ophthalmic solution) 0.02%
Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% 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.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

WARNINGS AND PRECAUTIONS
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 previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Clinical Trials 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 ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

Lactation
There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

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For more information, go to www.RHOPRESSA.com or call 1-855-AerieRx (1-855-237-4379).

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043

Letters

Haptic Length in Intrascleral Haptic Fixation

In reference to "Intrascleral Haptic Fixation as an Alternative to Sutures" (Clinical Update, May), I'd like to add that the causes of IOL tilt after flanged IOL fixation are asymmetric needle penetration and length mismatch between cornea diameter and haptic.

To prevent the former issue, I created an instrument to keep the needle penetration angle constant so that any surgeon who is unfamiliar with flanged IOL fixation can fix the IOL without tilt. (The tool is currently sold in Japan and is expected to be available in other countries within the year.)

When surgeons feel that the haptics are long, they should cut the haptics by 1-2 mm. In the glue technique, the haptics are externalized about 3 mm outside the eye. In the flanged technique, since the length of the haptics to be externalized is shorter, the scenario is the same as it would be when using the glue technique on haptics that had been cut slightly.

Shin Yamane, MD
Urafune-cho Minami-ku, Yokohama, Japan

Reusing Tonometers Increases Risk of Illness

"How to Disinfect and Calibrate Your Goldmann Applanation Tonometer" (Clinical Update, May) brings an important subject to the attention of eye care professionals. However, there are some inadvertent oversights in the article. The statement "no case of Creutzfeldt-Jakob disease has been linked to GAT" may not be entirely accurate.[1]

Additionally, the potential risk of transmission of hepatitis C via tonometry was not given enough attention. In the cohort of adults born between 1950 and 1960, the prevalence of hepatitis C infection is estimated to be 5%, and a majority of those infected are in a chronic carrier state without any disease manifestation.[2] The hepatitis C virus (HCV) is present in tears of infected individuals and can be infectious.[3] HCV is now the leading cause of death from infectious disease in the United States, and its associated mortality rate is expected to increase.[4]

The presence of HCV and other infectious agents in the tears of carriers is a public health issue and a potential occupational health hazard. As carriers manifest no symptoms of infection, any individual is potentially infectious. The only way to prevent transmission via tonometry is through the use of disposables.

We must protect the health of our patients and the public.

Francis Y. Falck Jr., MD, PhD, MS
Mystic, Conn.

1 Davanipour Z et al. *Br J Med Med Res.* 2014;4(12):2322-2333.
2 HCV epidemiology in the United States. Hepatitis C Online. https://www.hepatitisc.uw.edu/pdf/screening-diagnosis/epidemiology-us/core-concept/all;HCV.
3 Feucht H et al. *J Clin Microbiol.* 1995;33(8):2202-2203.
4 *The Clinical Advisor.* 2016;(6):6. https://issuu.com/clinicaladvisor/docs/ca0616_digital-edition.

A Response

We thank Dr. Falck for his interest in the article and agree with him that this subject is important.

Dr. Falck voices concern that the risk of prion disease transmission, such as Creutzfeldt-Jakob disease (CJD), is misrepresented in the article. In support, he quotes Davanipour et al.,[1] who establish that eye care providers may perform tonometry on asymptomatic carriers of CJD. However, the incidence of prion disease is low in the United States (approximately 1 case per million per year).[2-4] The risk of prion transmission by applanation tonometry is considered low to none by experts in the field,[5] who advise that instruments contaminated with high-risk tissue (i.e., brain, spinal cord, retina) from patients with known or suspected CJD require special precautions.[2] To date (June 18, 2018), there are no reports of prion disease transmission by tonometry. We agree with Dr. Falck that absolute elimination of prion transmission will require the use of disposable instruments.

Similarly, there are no reports of HCV transmission via tonometry to date (June 18, 2018). The prevalence of hepatitis C may be on the rise, but the virus is readily eliminated by 10% dilute bleach (hypochlorite), as are the human immunodeficiency virus, herpes simplex virus 1 and 2, and adenoviruses, with adenovirus being the greatest threat for nosocomial infection in the eye care setting.[6]

Philip P. Chen, MD, Seattle
Teresa C. Chen, MD, Boston
Anna K. Junk, MD, Miami
Shan C. Lin, MD, San Francisco
Kouros Nouri-Mahdavi, MD, Los Angeles
Sunita Radhakrishnan, MD, San Mateo, Calif.
Kuldev Singh, MD, MPH, Palo Alto, Calif.

1 Davanipour Z et al. *Br J Med Med Res.* 2014;4(12):2322-2333.
2 Rutala WA, Weber DJ. *Clin Infect Dis.* 2001;32(9):1348-1356.
3 CDC. Creutzfeldt-Jakob Disease, classic (CJD). Occurrence and transmission. https://www.cdc.gov/prions/cjd/occurrence-transmission.html.
4 CDC. Variant Creutzfeldt-Jakob disease (vCJD). vCJD cases reported in the US. https://www.cdc.gov/prions/vcjd/vcjd-reported.html.
5 Rutala WA, Weber DJ, Healthcare Infection Control Practices Advisory Committee. *Guideline for disinfection and sterilization in healthcare facilities, 2008.* Atlanta: CDC; 2008. https://www.cdc.gov/infectioncontrol/guidelines/disinfection/.
6 Junk AK et al. *Ophthalmology.* 2017;124(12):1867-1875.

Opinion

RUTH D. WILLIAMS, MD

Of Eminence-Based and Evidence-Based Medicine

David Lawrence Sackett, MD, was my kind of guy: He loved trout, Border collies, and reading—and he asked too many questions.

As a fourth-year medical student at the University of Illinois, Sackett was treating a teenager for hepatitis. The standard treatment was bed rest until the enlarged liver returned to a normal size. But the restless teenager was probably driving everyone crazy, and Sackett wondered about the evidence for imposing immobility. He scoured the U.S. Armed Forces Medical Library and found a study that randomized soldiers with hepatitis to rest or to normal activity. The outcomes were identical. He liberated his adolescent patient from imposed bed rest and launched a career in clinical epidemiology, a term he coined. Today, Sackett is known as "the father of evidence-based medicine."

Evidence-based medicine is a phrase we toss around with ease, but understanding what it means is illuminated by considering the phrase eminence-based medicine. Traditionally, medical decision-making was rooted in eminence-based medicine, which relied on the opinion of a prominent, seasoned physician. It depended on the clinical experience, advice, and opinions of our mentors, who we now call key opinion leaders (a term that should be retired because it reflects eminence-based thinking). Eminence-based decision-making has value, but it is flawed and limited. One cynic described clinical experience as "making the same mistakes with increasing confidence over an impressive number of years."[1]

For those of us who have practiced ophthalmology for decades, much of our training was rooted in eminence-based decision-making, even as evidence was emerging. I recall the buzz when the Diabetic Retinopathy Vitrectomy Study confirmed that early vitrectomy had better visual outcomes than conventional management for patients with severe vitreous hemorrhage secondary to diabetic retinopathy. But I also remember the words of Robert N. Shaffer, MD, one of our early eminent glaucoma specialists, who noted that most patients with intraocular pressures greater than 30 mm Hg eventually develop glaucomatous damage. Long before the randomized clinical trials of OHTS and EGPS even began, his comment was based in clinical experience, not in evidence, and he was mostly accurate.

Our emphasis on evidence-based medicine is described by 1 author as a shift from "trust in the experts" to "trust in the numbers."[2] However, Sackett recognized that both are necessary. In a 1996 editorial, he noted that overreliance on evidence can result in an inappropriate application, whereas overreliance on clinical expertise can result in out-of-date or detrimental care.[3] He identified the best approach as "integrating individual clinical expertise with the best available external clinical evidence from systematic research."

What, then, is evidence-based medicine? It is a process that coordinates conscientious and judicious use of modern, best evidence in making decisions about the care of an individual patient. Early critics of evidence-based medicine would find this definition disarming because it obviates cookbook medicine and ivory tower decrees. Evidence-based decisions marry the ancient art of medicine with the data-rich science of the modern age.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Sackett could not have foreseen this era of big data and how it will transform our clinical decision-making. Yet, the principles he elucidated—the integration of clinical expertise with scientific evidence—are more important than ever. The IRIS Registry, artificial intelligence, and image analysis will help us ask and answer clinical questions more efficiently. And, increasingly, we will have point-of-care tools that help us navigate the emerging and abundant evidence. Finally—and most importantly—the role of the physician will be enhanced, not diminished, as evidence and data grow.

1 O'Donnell M. *A Skeptic's Medical Dictionary.* London: BMJ Books, 1997.
2 Bolt TC, Huisman FG. *Ned Tijdschr Geneeskd.* 2015;159:A9297.
3 Sackett DL et al. *BMJ.* 1996:312(7023):71-72.

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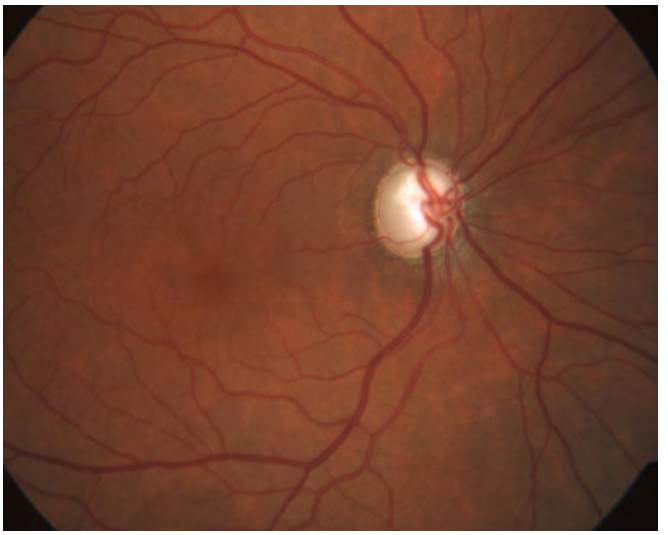


RETHINKING MANAGEMENT? *If the association with certain drug classes holds, patients with POAG (shown here) who are taking medications for depression or hypertension may need to be managed differently.*

GLAUCOMA

Systemic Drugs and POAG

A STUDY TO IDENTIFY ASSOCIATIONS between systemic medications and primary open-angle glaucoma (POAG) found that selective serotonin reuptake inhibitors (SSRIs), a common class of antidepressant medications, were associated with a 30% reduced risk of POAG. Conversely, calcium channel blockers, a common class of antihypertensive medications, were associated with a 26% increased risk of POAG.[1]

"These findings are so striking [that] they merit further research to help determine whether the association is causal. If so, this could significantly change how we manage glaucoma patients, particularly those with coexisting depression or hypertension," said Anthony P. Khawaja, PhD, FRCOphth, at Moorfields Eye Hospital in London.

A needle in a haystack. Drawing on a large insurance claims database covering Jan. 1, 2007, to Dec. 31, 2014, Dr. Khawaja and his colleagues identified more than 6,100 cases of POAG in patients who had undergone at least 1 glaucoma procedure. Cases were matched in a 1:5 ratio to 30,650 controls (defined as those who had undergone a cataract procedure but had no diagnosis of glaucoma).

The database identified 423 drug classes and 1,763 generic drugs that had been prescribed over a 5-year period prior to the glaucoma procedure or cataract surgery. "The huge sample size from this type of data meant we could test for associations with all known drugs and still find significant associations that survive correction for multiple testing," Dr. Khawaja said.

Further findings from systemic drugs. In addition to the SSRI and calcium channel blocker findings, the following associations emerged:

- Beta-blockers showed the second most significant protective association, particularly the generic metoprolol succinate. (Ophthalmic beta-blockers were excluded from the study.)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) showed a weaker—but still significant protective—association than SSRIs.
- There was a clear dose-response relationship for SSRIs, with progressively lower odds of POAG as the days of drug supply increased.
- There was no evidence of a dose response for calcium channel blockers.

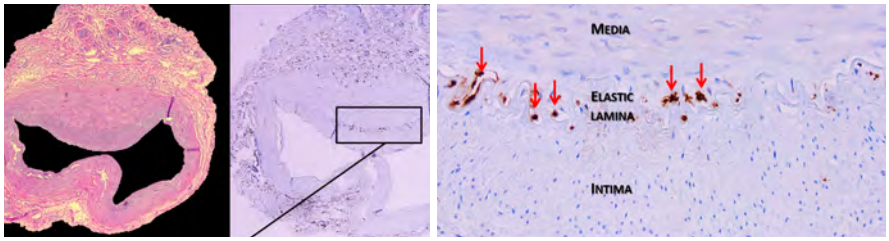
Affirmations and a surprise. The association between calcium channel blockers and an increased risk of POAG corroborated a finding in the Rotterdam Study.[2] "This is not a well-known association, but it is potentially very important, given the number of glaucoma patients on antihypertensive drugs," Dr. Khawaja said. "Calcium channel blockers have even been suggested as potential treatments for glaucoma, so to clarify this relationship with further research [will be] very important."

Given the known effects of beta-blockers on intraocular pressure, the beta-blocker finding was also not surprising. Rather, it validated the study design, Dr. Khawaja said. It also bolstered the credibility of the SSRI association, which has not been previously reported. As 22% of controls and 16% of cases were prescribed SSRIs, the association, if causal, could have a potential impact on POAG prevalence, he said.

Now Dr. Khawaja is looking for associations in other datasets. "If we replicate these findings and better characterize these associations, then further work leading toward possible pharmacological modifications of glaucoma risk will be warranted," he said. "We are many steps away, but it is conceivable that a trial of SSRIs to slow progression

of disease in POAG patients is warranted in the future." —*Miriam Karmel*

1 Zheng W et al. *Ophthalmology*. 2018;125(7):984-993.
2 Müskens RP et al. *Ophthalmology*. 2007;114(12):2221-2226.
Relevant financial disclosures—Dr. Khawaja: Novartis: C.



COMPARISON. *Routine hematoxylin and eosin (HE) stain of a histopathologic section of a temporal artery (left) shows irregular intima hyperplasia but no discrete multinucleated giant cells. Immunohistochemistry using CD68 antibody discloses positive cells at the level of the elastic lamina located in the media (muscularis) side with at least 5 positive cells (center and right, arrows).*

NEURO-OPHTHALMOLOGY

New Metric for Determining GCA Prognosis

WHICH GIANT CELL ARTERITIS (GCA) patients might benefit from early treatment with agents other than conventional steroid therapy?

A recent study offers a quantitative approach to answering that question.[1]

In this retrospective study, researchers assessed 42 GCA patients who had undergone temporal arterial biopsies (TABs), the gold standard for GCA diagnosis, at Houston Methodist Hospital in 2015.

The researchers reviewed patient charts for 4 variables: recurrence, number of days on glucocorticoids, referral to a rheumatologist, and placement on immunomodulatory therapy (IMT). They then correlated patients with features of healing/treated GCA and the 4 variables to the CD68 macrophage immunohistochemical marker found

CORNEA

Hyaluronic Acid Film Speeds Corneal Healing

PRECLINICAL TESTING OF A NOVEL HYDROGEL FILM made from cross-linked hyaluronic acid (HA) suggests that the polymer can rapidly accelerate the healing of large corneal burns, re-epithelializing them by 48 hours after the film is placed into the inferior fornix.[1]

Rapid recovery. The study, conducted in New Zealand white rabbits, found that corneas treated with the film, made of cross-linked, thiolated hyaluronic acid (CMHA-S), achieved complete re-epithelialization at 48 hours. In contrast, untreated eyes never had complete epithelial regrowth during 14 days of follow-up. The researchers found that both groups experienced some regression of epithelialization by the end of the study. However, the treated group retained significantly better re-epithelialization—83% versus 63% for untreated eyes.

Other findings. The treated eyes showed a 50% reduction in area of corneal opacity at the 14-day mark, while the untreated eyes had a 16% reduction. In addition, the treated eyes had significantly less edema, possibly because the compound inhibited the release of inflammatory mediators and cytokines.

Method of action. The cross-linking of CMHA-S into a translucent film enables the HA, long known for its protectant and lubricating properties, to be released slowly over time and to persist longer in the eye than a non–cross-linked liquid HA drop would, said Barbara Wirostko, MD, with EyeGate Pharmaceuticals and based in Salt Lake City.

"The film remains intact and in place longer than eyedrops and is less likely to break down. Thus, it may promote wound healing over an extended time period, especially in cases of severe trauma," she said. In the rabbit study, the film remained intact in the fornix for at least 14 days.

From animals to humans. A CMHA-S gel formulation has been available for several years as a treatment for dry eye and corneal wounds in animals (Remend, Bayer Animal Health), and EyeGate is developing it for use in humans, Dr. Wirostko said. In a pilot clinical study, post-PRK epithelial defects treated with the gel were, on average, 29% to 36.9% smaller as early as postop day 1 than those in eyes managed with a bandage contact lens and artificial tears.[2]

The company also is exploring the possibility that CMHA-S film can be used as a carrier for therapeutic molecules such as antibiotics. Dr. Wirostko said that this capability has already been demonstrated preclinically. "The film provides an alternative way of delivering the hyaluronic acid polymer and potential therapeutics in a sustained-released manner in severely traumatized eyes, potentially reducing or eliminating the frequent use of eyedrops." —*Linda Roach*

1 Griffith GL et al. *Burns*. 2018;44(5):1179-1186.
2 Durrie DS et al. *J Cataract Refract Surg.* 2018; 44(3):369-375.
Relevant financial disclosures—Dr. Wirostko: EyeGate: E,O.

Patricia Chévez-Barrios, MD

on the TAB specimens.

Slice metric. Using a metric of CD68+ cells per histologic slice, they found the following:

- Patients whose symptoms recurred at least once during follow-up had a greater number of CD68+ cells per slice compared to those with no recurrence (2.40 vs. 1.13, respectively).
- There was no statistical difference in cells/slice between patients who were referred to rheumatology and those who were not.
- Patients eventually placed on IMT had a greater number of cells/slice than did those who did not receive IMT (5.00 vs. 1.21, respectively).

"In this study, patients who had a more severe disease course [necessitating being placed on IMT] had a statistically significant greater number of CD68+ cells per slice than those patients not placed on IMT," said Patricia Chévez-Barrios, MD, at Houston Methodist Hospital.

A surprise. As for time on glucocorticoids, the researchers had hypothesized that the number of CD68+ cells/slice would decline over the course of treatment. In fact, there was no correlation between cells/slice and length of time on glucocorticoids, even beyond 40 days following initial treatment.

Clinical implications. Since most patients are on glucocorticoids at the time of TAB, quantification of CD68+ cells in TAB may help to identify patients with recalcitrant disease who cannot be managed with steroids alone, Dr. Chévez-Barrios said.

She suggested that pathologists could employ the metric to aid in determining severity of the disease course. "If the patient has an increased number of CD68+ cells per slice—greater than 2 cells per slice—then the patient might need to be referred for rheumatologic treatment sooner than a patient who has fewer than 2 cells per slice."

—Miriam Karmel

1 Sultan H et al. *Am J Ophthalmol.* Published online June 8, 2018.

Relevant financial disclosures—Dr. Chévez-Barrios: None.

RETINA

Thin RNFL Linked to Increased Risk of Dementia

THE LIST OF FAILED DRUG TRIALS for Alzheimer disease (AD) is lengthy and continues to grow, mainly because patients receiving treatment have an advanced case of the disease. Early detection is, therefore, key to finding a cure. But can an eye screening test help identify risk? A team of U.K. researchers explored the connection between the retina and dementia and found that a thin retinal nerve fiber layer (RNFL) might indicate future cognitive decline.[1]

The association. UK Biobank is a multicenter, community-based study of more than 30,000 U.K. residents aged 40 to 69 years. At enrollment, participants underwent optical coherence tomography (OCT) imaging, a physical examination, and cognitive testing. The research team found that worse cognitive performance was associated with a thinner RNFL at baseline, and those in the thinnest quintile of RNFLs were 11% more likely to fail at least 1 cognitive test. In addition, participants with an RNFL thickness in the 2 thinnest quintiles were almost twice as likely to have at least 1 test score be worse at follow-up.

Treatment implications. "Our findings suggest the retinal abnormalities that are identifiable in established dementia begin to manifest in the early stages of cognitive decline," said coauthor Paul J. Foster, PhD, FRCOphth, at Moorfields Eye Hospital and UCL Institute of Ophthalmology in London. And the earlier the detection, the better, he added. "Between 2002 and 2012, 99% of clinical trials of treatments for AD failed. A probable reason for this failure rate is that treatments are being provided to those patients who already have irreparable damage to the brain. By targeting people in the very early stages of cognitive change, it should be possible to design better clinical trials for treatments" that slow or stop further onset.

Supporting evidence. Similar results emerged in a Dutch study that explored the link between retinal neurodegeneration and dementia.[2] In the more than 5,000 study participants, OCT imaging showed that thinner ganglion cell–inner plexiform layers were associated with existing dementia, while thinner RNFLs were associated with an increased risk of developing dementia.

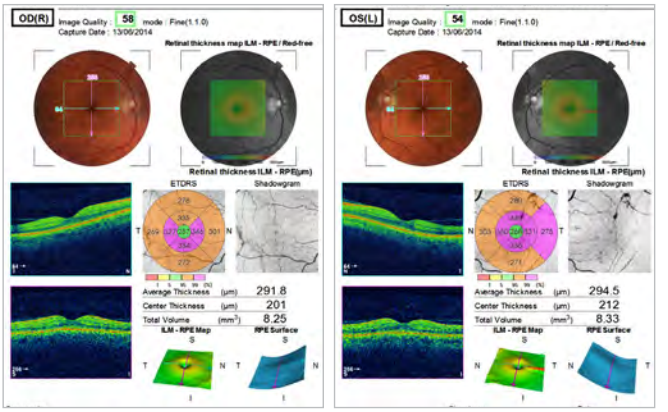
Taken together, these 2 studies suggest that retinal abnormalities—and possibly other ocular characteristics—may serve as unique preclinical biomarkers for dementia, specifically for AD. For clinicians and researchers, this could present an opportunity in the future to use OCT as an accessible and noninvasive tool to help monitor disease progression, evaluate treatment response, and shape eligibility determination for future clinical trials.

—Michael Mott

1 Ko F et al. *JAMA Neurol.* Published online June 25, 2018.

2 Mutlu U et al. *JAMA Neurol.* Published online June 25, 2018.

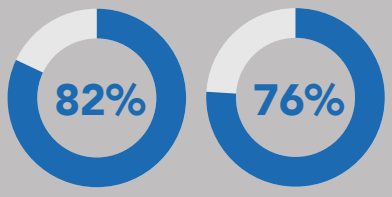
Relevant financial disclosures—Dr. Foster: None.



BIOMARKER. *This OCT map shows a thin RNFL, a potential red flag for dementia.*

Paul J. Foster, PhD, FRCOphth

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.



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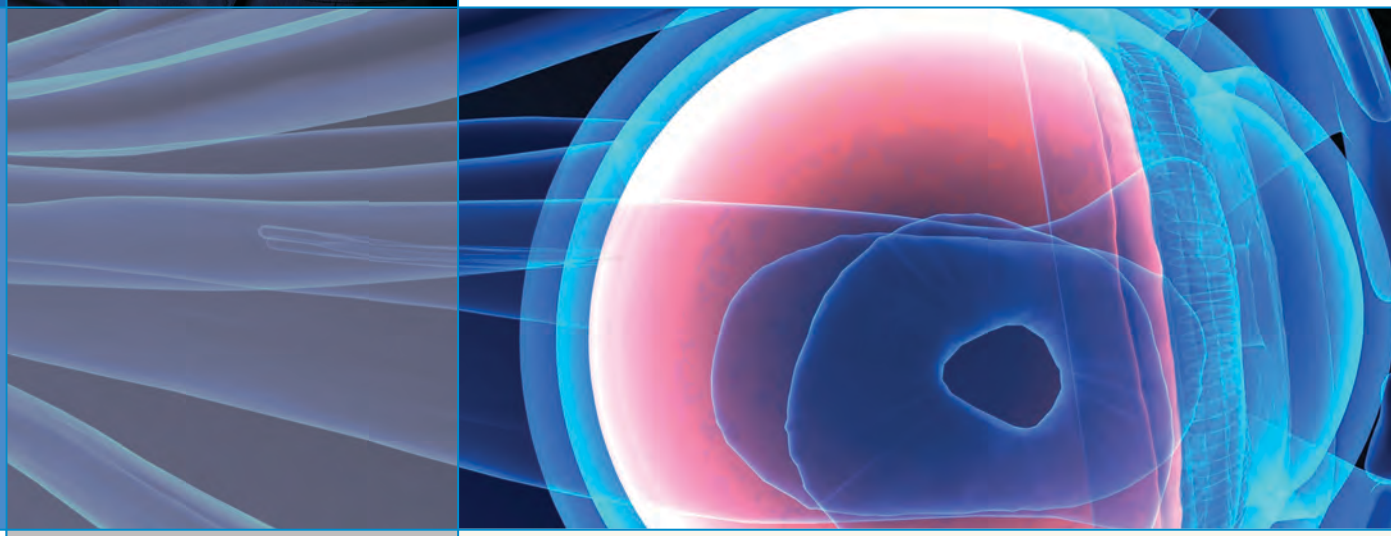

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

CRISPR-Based Genome Surgery for Retinitis Pigmentosa

September 2018

Tsai et al. set out to develop a universal gene therapy tool, based on CRISPR (clustered regularly interspaced short palindromic repeats) technology, to treat retinitis pigmentosa arising from mutations in rhodopsin. Their novel ablate-and-replace strategy appeared to ameliorate disease progression in a preclinical model, suggesting that it may have clinical potential as well.

This experimental study included 2 types of mutation knock-in mouse models: *Rho*^{P23H} and *Rho*^{D190N}. The experiment's premise was that autosomal-dominant *Rho* mutations cannot be remedied solely by conventional gene replacement or augmentation; a cure is possible only if the mutant allele is corrected or destroyed while the wild-type allele is kept intact.

Thus, for this study, the authors applied 2 sets of adeno-associated viruses (AAVs) simultaneously: One ablated the endogenous *Rho* gene by an improved CRISPR-based strategy while the other delivered exogenous complementary DNA expressing the wild-type Rho protein. For comparison purposes, a proportion of eyes received gene replacement only. Electroretinographic and histologic analyses were performed, and an unpaired 2-sided t test was used to compare mRNA levels and electroretinographic responses.

Three months after administration of gene therapy, the outer nuclear layer (ONL) of eyes that received ablation plus replacement was 17% to 36% thicker than the ONL of eyes that had replacement only.

Electroretinographic findings demonstrated that the combination of gene ablation and replacement resulted in superior preservation of a- and b-waves in both murine models.

To the authors' knowledge, their findings represent the first electrophysiologic evidence of the efficacy of CRISPR-based therapy for postmitotic neurons. The ablate-and-replace strategy can be applied in a mutation-independent manner and therefore may be a fiscally practical means to overcome allelic heterogeneity in many autosomal-dominant disorders.

Minor changes could be made to the dual AAV toolset to create a human version suitable for clinical trials. Ultimately, this strategy may permit universal treatment of patients, regardless of allelic status.

A 2-D Markov Model May Predict the Course of Glaucoma

September 2018

The ability to detect glaucoma and predict its course is crucial for effective management. **Song et al.** previously introduced a state-based 2-D continuous-time hidden Markov model (2-D CT HMM) to represent the pattern of detected glaucoma changes using structural and functional information simultaneously. In the present study, their goal was to determine the predictive performance of the model for detecting glaucomatous change in a real-world clinical setting, using retrospective longitudinal data.

The model proved promising for this purpose: Information from 1 visit signaled the clinical picture through 5 subsequent visits.

This longitudinal retrospective study included 134 patients (134 eyes) who had been diagnosed with or suspected of having glaucoma. The hidden state dimensions were thickness of the circumpapillary retinal nerve fiber layer by optical coherence tomography (structural) and the visual field index (VFI; functional).

In a second version of the model, mean deviation was substituted for VFI. The average follow-up period was 4.4 years, and the average number of visits was 7.1.

A subset of the data (107 of 134 eyes; 80%), obtained from all visits except the final one, was used to train the model (training set). The validation set comprised data for the other 27 eyes. Prediction accuracy was represented

as the percentage of correct predictions versus actual recorded states. The researchers also measured deviations of the predicted long-term detected change paths from the actual detected paths.

Results showed that the accuracy of glaucoma changes predicted for the training set was comparable to that of the validation set (57% and 68%, respectively).

The difference between predicted and actual detected paths of change remained similar throughout follow-up, with deviations actually decreasing (improving) over time. Because the sample size also declined with time, larger studies are needed to confirm the findings.

The 2-D CT HMM has the advantage of demonstrating nonlinear relationships between structural and functional degeneration. It may benefit glaucoma management by providing visually intelligible cues of changes in structure, function, or both. The model's ability to detect changes according to patient-specific data may pave the way for a new personalized-medicine approach to glaucoma assessment and treatment.

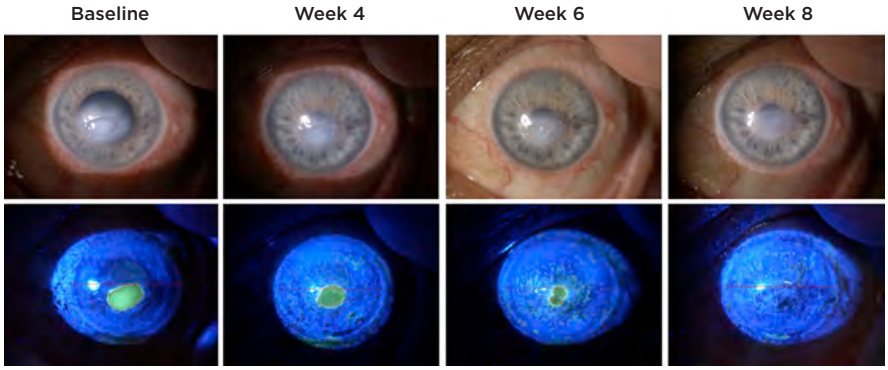
Neurotrophic Keratitis: Topical rhNGF Is Safe and Effective

September 2018

Bonini et al. assessed the safety and efficacy of topical recombinant human nerve growth factor (rhNGF) for treatment of moderate to severe neurotrophic keratitis (NK). Their results affirmed earlier safety findings and demonstrated the healing and neuroprotective effects of rhNGF in patients with this disease.

This multicenter phase 2 study was vehicle controlled, randomized, and double masked.

Patients with moderate (stage 2) or severe (stage 3) NK in 1 eye were eligible to participate. Those who met all inclusion criteria (N = 156) were assigned randomly (1:1:1) to receive rhNGF 10 µg/mL, rhNGF 20 µg/mL, or vehicle. The dosage for each study arm was 6 drops per day for 8 weeks. Follow-up ensued for at least 48 weeks.



KERATITIS TREATMENT. *This patient—who had an oval, acentral, neurotrophic corneal lesion—was treated with 20 µg/ml rhNGF. Photographs taken from baseline through week 8 under diffuse white light (top row) and cobalt-blue light (bottom row) illumination.*

The main measure of efficacy was corneal healing, defined as total lesion-area diameter <0.5 mm by fluorescein staining. Assessments were made by centralized masked readers at week 4 of follow-up (primary endpoint) and again at week 8 (key secondary endpoint). Corneal healing also was assessed post hoc, using a more conservative measure (0-mm stained lesion area and no other visible staining). The primary variable for safety assessment was the incidence of adverse events.

By the 4-week follow-up, corneal healing had occurred in 54.9% of the 10-µg/mL rhNGF group, 58% of the 20-µg/mL rhNGF group, and 19.6% of the vehicle-control group. By week 8, the respective rates of corneal healing were 74.5%, 74%, and 43.1%, respectively.

Post hoc analysis by the more conservative measure also demonstrated significant differences, at both time points, between active treatment and vehicle control. More than 96% of patients whose cornea healed from rhNGF treatment remained free of recurrence throughout follow-up.

Few patients experienced adverse events (AEs), most of which were local, mild, and transient, and did not require cessation of treatment. The highest incidence of AEs was in the control group.

Findings of this study indicate that the benefits of rhNGF outweighed the risks for patients with moderate to severe NK.

The rhNGF treatment also holds promise for other ophthalmic conditions with neurodegenerative components, such as glaucoma, macular degeneration, and retinitis pigmentosa.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Natural History of Geographic Atrophy

September 2018

In geographic atrophy (GA) clinical trials, a change in a GA measure is usually selected as a primary outcome for evaluating treatment efficacy. However, estimates of GA progression rates in untreated eyes vary widely. **Shen et al.** evaluated the natural progression pattern of GA secondary to nonexudative age-related macular degeneration (AMD) in untreated eyes. They found that the radius of GA lesions increases linearly with time, with a high level of correlation across a wide range of studies.

For this review—believed to be the first meta-analysis on the topic—the authors included 25 studies with data from 2,942 eyes. They analyzed the data using the area linear model, the radius linear model (RLM), and the area exponential model. Of these 3 models, the RLM—in which GA radius grows linearly with time—proved to have the strongest predictive performance. A horizontal translation factor was added to account for the fact that participants entered into the individual studies at

different time points in the history of their disease.

The results showed that GA radius continues to increase at a constant rate of 0.163 mm per year and that this growth rate is consistent across different age groups. The RLM also predicted the age of onset of GA as 67.4 ± 5.2 years.

Thus, the authors calculated, if a patient with GA presents at 67.4 years, the radius of the GA lesion would be 3.26 mm (20 x 0.163) 2 decades later. This is consistent with observations from clinical experience, as patients with GA often have lesions that occupy most of the area within the arcades at the latest stages of their disease.

The authors noted that this analysis only had data in GA sizes ranging from 2.46 to 20.3 mm^2; thus, they said, they do not know if a similar fit is present for GA sizes outside of this range. Nonetheless, they suggested that the RLM be used in future clinical trials designed to evaluate the effect of a treatment on GA progression.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Inner Nuclear Layer Thickness, Metamorphopsia, and Tangential Retinal Displacement

September 2018

Metamorphopsia is a common early feature of macular diseases such as central serous chorioretinopathy, age-related macular degeneration, and epiretinal membrane (ERM). In a retrospective clinical study, **Ichikawa et al.** looked at inner nuclear layer (INL) thickness in relation to metamorphopsia and tangential retinal displacement in ERM. They found INL thickness to be a useful biomarker for metamorphopsia, as well as an indicator of tangential retinal displacement in ERM.

The study was a consecutive interventional series of 50 patients (50 eyes) who received surgery for ERM. M-charts were used to measure metamorphopsia. Measurements of INL thickness, outer retinal layer (ORL) thickness, and distances between the intersections of 2 sets of retinal vessels were obtained from Spectralis optical coherence tomography (Heidelberg Engineering) and infrared images.

Outcomes of interest were correlations of INL and ORL thickness with M-chart scores and retinal displacement distances.

The authors noted strong correlations between preoperative INL thickness and the metamorphopsia scores obtained preoperatively and 3 months postoperatively. Moreover, INL thickness at baseline and its change from baseline to 3 months correlated significantly with vertical retinal displacement observed 3 months postoperatively (both $p < .001$). Neither preoperative nor postoperative ORL thickness was found to correlate with preoperative or postoperative metamorphopsia scores.

Therefore, the authors proposed the utility of INL thickness as a biomarker for the degree of metamorphopsia both before and after ERM surgery. Their findings suggest that changes in the inner retinal layer, which cause distortion of Müller cells, play a large role in the development of metamorphopsia, thus providing further evidence that Müller cells function as optical fibers in the retina. However, the precise mechanisms by which retinal layer shrinkage generates metamorphopsia have not been determined.

Even when ERM surgery is successful, many patients will experience aniseikonia and metamorphopsia afterward. Hence, the authors recommend exploration of more efficient ways to correct irregular positions of retinal Müller cells.

Corneal Ectasia and Chronic Stevens-Johnson Syndrome

September 2018

In a recent case series, corneal ectasia was an incidental finding in patients with Stevens-Johnson syndrome (SJS), an inflammatory disease affecting skin and mucous membranes. Subsequently, **Maharana et al.** assessed topographic changes in patients with chronic SJS and concluded that corneal ectasia is a common but often-missed contributor to poor visual acuity.

This prospective observational study included 30 eyes of 15 consecutive patients (median age, 26 years; 11 males) with chronic SJS who were referred to a cornea clinic. In all cases, SJS was caused by medication-induced hypersensitivity reaction. The median time from disease onset to assessment was 7 years (range, 1-27 years).

The authors used a Scheimpflug system (Pentacam-HR, Oculus) for enhanced detection of corneal ectasia. Repeat imaging was performed until a good scan was obtained. Primary outcomes were best-corrected distance visual acuity (BCDVA), maximum corneal curvature (Kmax), anterior and posterior elevations, thinnest pachymetry, and Sotozono severity score. Final analyses were performed on 21 eyes.

At presentation, median BCDVA was 0.8 logMAR units, Schirmer score was 0 mm, and Sotozono score was 11. Tomography revealed corneal ectasia (Kmax >48 D) in 76.2% of eyes (mean Kmax, 58.37 ± 14.89 D). Front and back elevations on Belin/Ambrósio ectasia display were 42 µm (range, 10-176 µm) and 267 µm (range, 15-2,392 µm), respectively. Mean pachymetry was 377.76 ± 165.05 µm (range, 133-448 µm). The point of maximum ectasia was peripheral in 57.1% of eyes, central in 23.8%, and both peripheral and central in 19.1%. Spearman correlations indicated that deterioration of BCDVA and elevation of Kmax were linked to higher Sotozono severity scores. Associations between disease severity and presentation time, thinnest pachymetry, or anterior/posterior elevations were not significant.

According to the authors, their findings suggest that higher Sotozono scores denote more severe ectasia and that posterior elevation ≥15 µm signals early ectasia. However, validation is needed.

To properly manage SJS and its long-term effects, they advocate checking for corneal ectasia in all patients with the syndrome, especially if reduced visual acuity seems disproportionate to disease severity.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Is Pediatric Atopic Dermatitis Associated With Cataract?

August 2018

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that affects up to 20% of children in industrialized countries. Although the condition has been linked to various ocular complications, whether pediatric AD is associated with cataract is unknown. **Jeon et al.** investigated this matter in a Korean pediatric population. They found that, although the association appears to be rare, pediatric AD carries a higher-than-normal risk for cataract surgery.

For this population-based retrospective longitudinal study, the authors extracted nationally representative data from the Korean National Health Insurance Service database for a 12-year period (2002-2013).

Each incident case of AD or severe AD in a person <20 years of age was matched to 4 controls, using propensity scores derived from age, sex, residential area, and household income. Main outcome measures were incidence probabilities of cataract development and cataract surgery for patients with AD and controls, which were compared using Kaplan-Meier methods and log-rank tests. Cox proportional hazard models, fitted for cataract and cataract surgery, were applied to determine risk factors in the matched cohort.

Among the 34,375 patients with incident AD (mean age, 3.47; 47% female), severe AD was present in 3,734 (10.9%). The total number of matched controls was 137,500. The incidence of cataract development was similar for the AD and control groups (0.216% vs. 0.227%) and for patients with severe AD and their controls (0.520% vs. 0.276%).

Cataract surgery was performed more frequently in the AD cohort than in the control group (0.075% vs. 0.041%) and more often in patients with severe AD than their controls (0.221% vs. 0.070%). Severe AD was associated with cataract development and the need for cataract surgery.

The authors concluded that the absolute risk of cataract is rare, with or without AD. However, their findings suggest that patients with AD are more likely to require surgery for cataract and that this is particularly true for those with severe AD.

Trends in Traumatic Pediatric Acute Ocular Injury

August 2018

Understanding national trends in pediatric eye injury may guide efforts to prevent ocular trauma.

Focusing on mechanisms of injury and their association with demographic factors and the risk of vision loss, **Matsa et al.** reviewed prevalence data and noted trends for a 9-year span. During that period, the rate of pediatric ocular injuries associated with visits to the emergency department (ED) decreased substantially and was consistent among demographic characteristics, patterns of injury, and vision-loss risk categories.

For their research, the authors used a stratified U.S. sample of data from ED visits for acute traumatic ocular injury, occurring from 2006 through 2014. The study cohort consisted of 376,040 patients from birth to 17 years of age. Collected data included demographic and clinical characteristics. Temporal trends were explored and compared, including the incidence of ocular injury, risk of vision loss, and mechanism of injury.

Diagnoses were assigned to 1 of 3 risk categories for vision loss, depending on the injury location: high risk (pathognomonic), variable risk (need for injury monitoring), or low risk (vision sparing was anticipated). Data analysis was completed in 2018.

Between 2006 and 2014, the proportion of pediatric acute ocular injuries presenting to EDs declined by 26.1% and was similar across demographic variables, injury patterns, categories of vision-loss risk, and most mechanisms of injury.

Among injuries with a high risk of vision loss, the greatest declines were observed for motor vehicle trauma (−79.8%) and gunshot wounds (−68.5%). Injured children were more often male (63%) and in the youngest age group (birth to 4 years: 35.3%). Injuries commonly resulted from a strike to the eye (22.5%) and affected the adnexa (43.7%). Most injuries (84.2%) were low risk for vision loss; only 1.3% were high risk. Types of injury that increased during the study span involved sports (+12.8%) or household/domestic activities (+20.7%).

The authors suggest further investigation to pinpoint the initiatives that may be contributing to the observed decline in pediatric ocular injury and to identify interventions to reduce the most common injuries and those with high risk of visual impairment.

Genetic Variants Linked to Poor AMD Treatment Outcomes

August 2018

Currently, the most effective treatment for neovascular age-related macular degeneration (AMD) is intravitreal injection of anti–vascular endothelial growth factor (VEGF) drugs. However, visual results vary considerably. **Lorés-Motta et al.** conducted a multicenter genome-wide study aimed at identifying genetic factors associated with this variability. They found that the poorest visual acuity (VA) outcomes correlated with protein-altering variants in the *C10orf88* and *UNC93B1* genes.

Their study included 678 patients with wet AMD for whom genome-wide genotyping data were gathered in the discovery phase. In addition, genotyping was performed in the replication phase for another 1,380 patients with the disease. All participants received a loading dose of bevacizumab or ranibizumab, consisting of 3 injections given monthly. The primary outcome was the change in VA from baseline to completion of therapy.

The mean age of the entire study population was 78 years. All patients in the discovery cohort and most of those in the replication cohort were of European descent.

At baseline, the mean (standard

deviation) VA score was 51.3 (20.3) letters according to the Early Treatment Diabetic Retinopathy Study (ETDRS) system. After the third injection, the mean gain in VA was 5.1 (13.9) ETDRS letters, denoting improvement of 1 full line.

Genome-wide analyses of common single variants showed that 5 independent loci were associated with a p value below 10×10^{-5}. After replication and meta-analysis of the lead variants, rs12138564 in the *CCT3* gene was nominally associated with a better VA outcome (letter gain of 1.7). The gene-based optimal unified sequence kernel association test of rare variants showed genome-wide significant associations for the *C10orf88* and *UNC93B1*, both of which led to poorer outcomes. Patients with a rare variant in *C10orf88* or *UNC93B1* lost a mean of 30.6 letters (6.09 lines) or 26.5 letters (5.29 lines), respectively.

Although the findings suggest that rare protein-altering genetic variants may signal a poor visual response to anti-VEGF therapy in patients with neovascular AMD, further investigations are warranted. Information gleaned from this study and similar research may help to personalize management.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Oral or IV Corticosteroid Treatment of Optic Neuritis

JAMA Neurology
2018;75(6):690-696

Intravenous (IV) administration of corticosteroids is the standard of care for acute optic neuritis, but it can be costly and inconvenient. In an investigator-masked randomized study, **Morrow et al.** sought to determine whether oral administration of a bioequivalent oral corticosteroid would be as effective as IV administration in the management of this condition. The authors found that recovery of vision was similar for the 2 treatment arms.

Fifty-five adults presenting within 14 days of optic neuritis onset were enrolled in the study, which included a 6-month follow-up period. Participants were assigned randomly (1:1) to receive IV methylprednisolone sodium succinate (1,000 mg) or oral prednisone (1,250 mg) and were unmasked to treatment assignment. Each treatment was administered daily for 3 days. The selected oral dose was based on evidence of its bioequivalence to 1,000 mg of IV methylprednisolone in persons with multiple sclerosis.

IV treatment was administered at a hospital outpatient infusion center—or, when possible, at a hospital outpatient infusion center for the first dose and at home for subsequent doses. Patients in the oral group received 75 tablets of 50-mg prednisone to be consumed at home (25 tablets per day). The primary outcome was recovery of the latency of the P100 component of the visual evoked potential at 6 months. Secondary outcomes were P100 latency at 1 month and best-corrected visual acuity (BCVA) at 1 and 6 months.

The final analysis cohort included 45 patients (23 in the IV group and 22 in the oral group).

At 6 months, mean P100 latency had improved by 62.9 ms (from 181.9-119.0 ms) in the IV group and by 66.7 ms (from 200.5-133.8 ms) in the oral group. Also similar was P100 latency recovery at 1 month and BCVA at months 1 and 6, including low-contrast scores.

The authors concluded that bioequivalent oral doses of IV corticosteroids appear to be suitable treatment for optic neuritis. As demonstrated in other studies, patients are likely to prefer the cost and convenience of oral medication.

First Human Study of Intraocular Robotic Surgery

Nature Biomedical Engineering
Published online June 18, 2018

Edwards et al. have pioneered a first-in-human study of remotely controlled robot-assisted retinal surgery performed through a telemanipulation device. Their findings indicate that such a system, although still in its infancy for human use, has potential to achieve the precision warranted for many intraocular procedures. Specifically, surgical outcomes with the robotic system were comparable to those of manual surgery, but operating time was longer with the new technology.

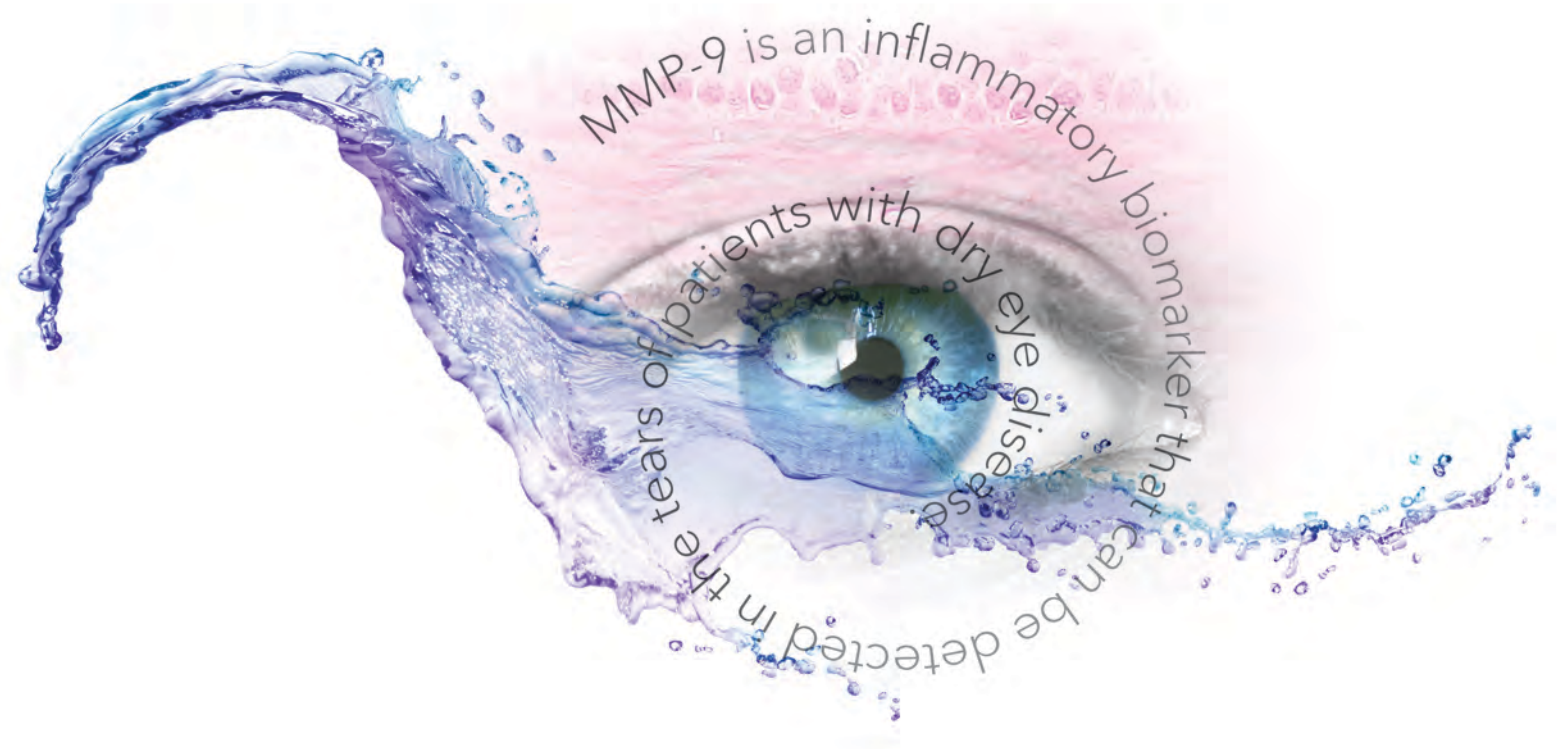
For this double-armed study, 12 patients who required removal of an epiretinal or inner limiting membrane peel for macular hole repair were assigned randomly to receive robot-assisted surgery or manual retinal surgery (all procedures were conducted with the patients under general anesthesia).

The robotic system used by the investigators (Preceyes) had already been applied successfully in animals. The system combines a motion controller, held by the surgeon, with an instrument manipulator that can be fitted with a host of microsurgical instruments. Features include tremor filtering, adjustable virtual boundary, dynamic motion scaling, and a clutch mechanism that can freeze the position of the instrument inside the eye. In pigs, the system was able to cannulate and deliver drugs into retinal venules of approximately 80 µm in diameter, which would not be possible with manual surgery.

Main outcomes for the present study in humans were surgical success, duration of surgery, and the amount of retinal microtrauma (as a proxy for safety).

Surgical success and the amount of retinal microtrauma were comparable for the 2 study groups. However, dissection time was much longer with robotic surgery (4 minutes, 55 seconds vs. 1 minute, 20 seconds). To simulate potential use for subretinal gene therapy, the authors also used the robotic system to inject recombinant tissue plasminogen activator subretinally in 3 patients who had acute central vision loss caused by subretinal hemorrhage, secondary to age-related macular degeneration. These patients received local anesthesia. The robotic system accomplished the task, effectively displacing sight-threatening hemorrhage in their eyes.

—Summaries by Lynda Seminara



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Drug Update: Vyzulta and Rhopressa

After an extended drought, 2 new—and much anticipated—glaucoma drugs are now on the market. "We've had a long stretch without any new glaucoma medications," said Ahmad A. Aref, MD, at the University of Illinois College of Medicine in Chicago. "Now, at the same time, we have 2 relatively low-risk ways to decrease the threat of irreversible vision loss from glaucoma. That's a big deal."

In late 2017, the FDA approved latanoprostene bunod ophthalmic solution (Vyzulta, 0.024%; Bausch + Lomb) and netarsudil ophthalmic solution (Rhopressa, 0.02%; Aerie Pharmaceuticals) for reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1,2] "Rhopressa and Vyzulta have stolen the limelight," said Dr. Aref. "It will be interesting to see how this plays out, especially from a payer perspective."

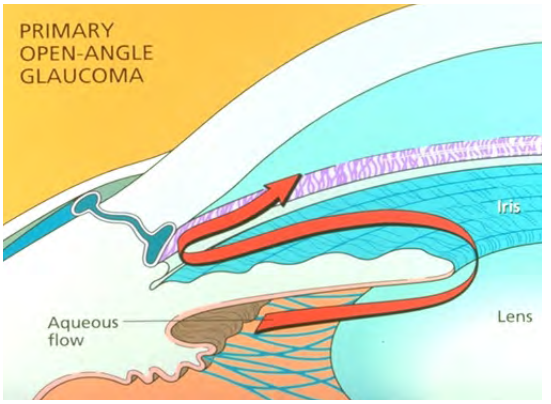
Here's a look at the 2 drugs, plus an update on drugs in the pipeline (see "From Drought to Flood?" on page 28).

Vyzulta: Releasing Nitric Oxide

A once-daily eyedrop, Vyzulta is a prostaglandin analog that is metabolized into 2 moieties and regulates IOP through both the trabecular outflow and uveoscleral outflow pathways, said Robert N. Weinreb, MD, at the University of California, San Diego.

Dual mechanism of action. "One component is latanoprost, our most efficacious first-line agent for glaucoma, which has been on the market for more than 2 decades and removes fluid through the uveoscleral outflow pathway," said Dr. Aref.

The second component is butanediol mononitrate, which releases nitric oxide (NO), Dr. Weinreb said. "Nitric oxide induces cell relaxation in the trabecular meshwork by activating the nitric oxide–cyclic guanosine monophosphate signaling pathway, which is thought to lead to a widening of the intercellular spaces in the trabecular meshwork, thereby increasing the conventional outflow."



METHOD OF ACTION. *Through novel mechanisms, both Vyzulta and Rhopressa improve outflow of aqueous through the trabecular meshwork. Each medication is a once-daily eyedrop.*

The NO component is the unique aspect of the drug's mechanism of action, giving it a bit of an efficacy edge in lowering IOP over latanoprost alone, said Dr. Aref. When different concentrations of Vyzulta were compared against latanoprost alone,[3] only higher concentrations of Vyzulta were found appreciably more effective, he said. "This suggests that the nitric oxide was responsible for the incremental efficacy."

Efficacy. A veritable space race of studies has examined the effectiveness and safety of Vyzulta. Results of the LUNAR and APOLLO studies showed that Vyzulta was more effective than timolol. Although the findings were not a surprise, the noninferiority study was necessary, said Harry A. Quigley, MD, at the Wilmer Eye Institute in Baltimore. "Before bringing a glaucoma drug to market, the FDA requires that it work at least as well as timolol."

A study published earlier this year[4] also looked at the pooled results of all studies comparing Vyzulta to timolol over 12 months, said Dr. Aref. "With Vyzulta, the percentage reduction in IOP from baseline was 32%. That's a sizable reduction with just 1 eyedrop dosed once a day."

The VOYAGER study compared Vyzulta to latanoprost alone. Among the Vyzulta studies, Dr. Aref considers it most significant because latanoprost is the clinical benchmark against which other glaucoma drugs are compared. In this study, Vyzulta was associated on average with 1.2 mm Hg of additional

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **AHMAD A. AREF, MD, HARRY A. QUIGLEY, MD,** AND **ROBERT N. WEINREB, MD.**

IOP lowering compared to latanoprost.[3]

"This is fairly significant," said Dr. Aref, "because epidemiologic studies have shown that for every 1 mm Hg incremental decrease in IOP, you can reduce the risk of visual field loss related to glaucoma by about 10%."

Other studies have also looked at 24-hour lowering of IOP, said Dr. Weinreb, indicating that Vyzulta is effective both day and night.[5]

Safety and tolerability. "In a phase 2 clinical trial, Vyzulta was very similar to latanoprost in terms of tolerability," said Dr. Weinreb. Most side effects, such as irritation and eyelash changes, were mild, and hyperemia was similar in both groups. "But, of course, the drug is only recently available," he said.

Indeed, wider clinical use may eventually uncover issues with Vyzulta, as has happened with other ophthalmic drugs. Dr. Quigley cited timolol as a case in point: Individuals with dry eyes were not admitted to the study, he said, but once the drug came out of controlled trials into the real world, beta-blockers were found to be challenging for people with dry eyes.

Role for Vyzulta. Vyzulta is appropriate as a first-line treatment option for patients with open-angle [glaucoma] or ocular hypertension, Dr. Weinreb said. Many patients may also be put on Vyzulta as a second-line therapy in an attempt to avoid surgery, Dr. Quigley said. "If you tell patients they have to take this new drug or have surgery, you'll likely increase their adherence."

Rhopressa: First ROCK Inhibitor

Like Vyzulta, Rhopressa is a once-daily eyedrop. However, as a Rho kinase (ROCK) inhibitor, it represents the first new class of glaucoma drugs in more than 20 years.

Triple mechanism of action. Rhopressa possesses 3 different mechanisms of action in a single agent, said Dr. Aref. The drug decreases production of fluid and decreases episcleral venous pressure, he said. Rhopressa also lowers the resistance to outflow through the trabecular meshwork.

Among its effects, Rhopressa works at the cellular level within the trabecular network, and it has a novel mechanism of action there, said Dr. Weinreb. "The drug promotes actin-myosin contraction and increases actin stress fibers and focal adhesions in the trabecular meshwork to improve the outflow of aqueous humor."

Efficacy. ROCK inhibitors are supported by extensive basic science research showing improvement of outflow through the trabecular meshwork, predominantly for glaucoma patients with higher-than-normal pressures, said Dr. Quigley, but they may also be effective for those with lower pressures. Few studies have examined those with pressures below 20 mm Hg at the time of diagnosis, he said, which is about half of those who have open-angle glaucoma with optic nerve damage.

However, noninferiority timolol studies—ROCKET-1 and ROCKET-2—included lower pressures in their study groups.[6] These studies found timolol was not better than Rhopressa for patients with baseline eye pressure less than 25 mm Hg over a 3-month time period, said Dr. Aref. "Rhopressa showed consistent IOP reduction, about 5 mm Hg across a range of baseline pressures," said Dr. Weinreb, "particularly notable in patients with low baseline IOP."

Safety and tolerability. In ROCKET-1 and ROCKET-2, about half the patients experienced conjunctival hyperemia, the most common side effect. This redness may result from one of Rhopressa's mechanisms of action,

From Drought to Flood?

Here's a sample of drugs and devices in the glaucoma pipeline.

Roclatan. In May, Aerie filed a new drug application to the FDA for Roclatan, its once-daily combination of netarsudil and latanoprost. "That could be very attractive, because the fixed-dose combination has performed significantly better than either netarsudil or latanoprost alone," said Dr. Weinreb.

"To help with the adherence issue, we've wanted to see drugs combined with latanoprost for a long time," Dr. Quigley commented. "This could be beneficial for those who need more than the prostaglandin alone." The drug is definitely needed, added Dr. Aref. "It might be a very good first-line option for our patients. The big question is whether the combination agent is more efficacious than Vyzulta."

Sustained-release options. In trials under highly controlled conditions, patients only use 72% of their topical glaucoma medications, said Dr. Quigley, but the estimate in the real world is closer to 50%. If clinicians could deliver a sustained-release drug in the office that lasted 6 months, he said, "it would only have to be half as effective as the eyedrop to be more effective overall. And it would also be there in a constant dose instead of in a whopping high dose followed by none at all 24 hours later." Because sustained-release drugs do sacrifice efficacy to some degree, they may not be a first-line therapy for those without adherence issues, said Dr. Aref.

In preclinical studies, Dr. Quigley and his colleagues have experimented with subconjunctival delivery of biodegradable polymer microparticle formulations of dorzolamide. "Other research is ongoing with a variety of methods for sustained delivery," he said.

Allergan has a biodegradable sustained-release bimatoprost implant in clinical trials that is injected into the anterior chamber, said Dr. Weinreb. An ongoing phase 3 clinical trial may answer questions about its length of efficacy and impacts on the cornea.

Microdose spray. A new technology by Eyenovia uses a variation on high-resolution inkjet printing technology that allows patients to self-administer small doses of drug to the eye, said Dr. Weinreb. This has the potential to reduce side effects and increase safety and tolerability, he said, adding that the company is planning phase 3 studies.

which is relaxation of the blood vessels, said Dr. Aref.

During the drug's early days on the market, Dr. Quigley expected reports of redness to be more substantive than those noted during the clinical trials, as trial participants tend to be less tolerant of side effects. "If you have lots of redness in phase 2 and 3 trials, it won't get better once the drug is used in the real world," he said.

But now that Rhopressa has been in use for several months, "the redness issues have been much less than what I would have expected from clinical trial data," Dr. Aref said. "I currently let patients know to expect some degreee of redness that will likely wane over the first few weeks of therapy. That expectation allows patients to tolerate the agent a little better. In practice, it is unlikely for patients to discontinue therapy for this reason alone."

Other common side effects noted during clinical trials were discomfort with drug administration and conjunctival hemorrhage—typically mild petechiae at the limbus, said Dr. Weinreb. "Twenty percent of patients also experienced corneal verticillata. This side effect does not seem to affect vision and is reversible with discontinuation of the drug."

Dr. Quigley raised concerns about the safety of drugs like Rhopressa that alter the sclera. Do they have an impact on retinal ganglion cell axons? "It is extremely important to ensure that any negative effect is negligible or that the alteration is potentially beneficial to the ganglion cells," he said. "However, we worried about the same thing with latanoprost, and after 20 years, there is no indication that the protective effect of IOP lowering is lessened by a detrimental effect that increases glaucoma damage."

Role for Rhopressa. "Rhopressa is likely to be a useful second-line treatment," said Dr. Weinreb. "It is not quite as effective as the prostaglandins and might not be as well tolerated." However, secondary types of glaucoma, such as steroid-induced glaucoma, may be amenable to Rhopressa because of its unique mechanism of action," Dr. Aref noted. "Steroids increase resistance to outflow through the trabecular meshwork, but Rhopressa works to decrease it."

A Note on Cost

When Vyzulta initially entered the market, Dr. Quigley said, his office staff was spending "a lot of time and effort" trying to get the drug for patients, as most pharmacy plans did not cover it at that point.

But coverage and reimbursement are active processes, and costs are shifting rapidly. For instance, in late June, Rhopressa was added to the preferred panel for a major plan, and the price fell to $25 per bottle for those patients.

Even as more drug plans add Vyzulta and Rhopressa, cost will be a critical issue for clinicians to discuss with their patients. In particular, the cost differential between Vyzulta and latanoprost —which has been a generic agent for about 5 years—may need to be part of the conversation, Dr. Aref noted.

1 Food and Drug Administration. Vyzulta: Highlights of prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/207795Orig1s000lbl.pdf.

2 Food and Drug Administration. Rhopressa: Highlights of prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/208254lbl.pdf.

3 Weinreb RN et al. *Br J Ophthalmol.* 2015;99(6):738-745.

4 Weinreb RN et al. *J Glaucoma.* 2018;27(1):7-15.

5 Arale M et al. *Adv Ther.* 2015;32(11):1128-1139.

6 Serle JB et al. *Am J Ophthalmol.* 2018;186:116-127.

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Dr. Quigley is professor of ophthalmology at the Johns Hopkins Wilmer Eye Institute in Baltimore. *Relevant financial disclosures: None.*

Dr. Weinreb is chairman and professor of ophthalmology at the University of California, San Diego; director of the Shiley Eye Institute in San Diego; and director of the Hamilton Glaucoma Center in La Jolla, Calif. *Relevant financial disclosures: Aerie Pharmaceuticals: C; Allergan: C; Bausch + Lomb: C; Eyenovia: C.*

See the disclosure key, page 8. **For full disclosures,** view this article at aao.org/eyenet.

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Programs

Saturday, Oct. 27 **Diabetic Eye Disease: Clinical Challenges and Practical Tips for Multidisciplinary Disease Management**

Speakers: Robert Busch, MD (endocrinologist), John W. Kitchens, MD

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Sunday, Oct. 28 **INSiiGHTS AT AAO: A Spotlight on Dry Eye Treatment**

Speakers: Eric D. Donnenfeld, MD, Edward J. Holland, MD, Terry Kim, MD

Presented by Shire

Monday, Oct. 29 **Cataract Surgery: Life is Beautiful When the Pupil Behaves**

Speakers: Eric D. Donnenfeld, MD, Cynthia A. Matossian, MD, FACS, Steven M. Silverstein, MD, Denise M. Visco, MD, Keith A. Walter, MD

Presented by Omeros Corporation, and designed for U.S. cataract surgeons.

Check aao.org/eyenet/corporate-events for updated program information.

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Intraoperative OCT: An Emerging Technology

Intraoperative optical coherence tomography (iOCT) is a technology that allows ophthalmic surgeons to evaluate the effects of surgical manipulations in real time. Just as OCT now commonly guides decisions in the clinic, iOCT may become a key asset in the surgical setting.[1]

"I was initially skeptical about the value of intraoperative OCT," said Andreas K. Lauer, MD, at Casey Eye Institute at Oregon Health & Science University in Portland. "Now, I see that it is really indispensable, especially for gene therapy, and for other conditions as well."

Evolution of iOCT

The first step, the development of a handheld, portable OCT system, was a huge leap forward in the evolution of intraoperative OCT, said Justis P. Ehlers, MD, at the Cleveland Clinic in Ohio.

Handheld OCT. Before handheld OCT, surgeons who wanted intraoperative OCT would use conventional office-based OCT systems. This, said Dr. Ehlers, "required gymnastics in the OR to turn a system on its side to take images."

Although handheld systems were an improvement over these improvisational techniques, the newer systems weren't perfect, he said. "They came with significant challenges around repeatability of the scan, ability to aim at the area of interest, and delays in taking images during surgery."

Dr. Lauer added that despite the advantage of its high resolution, handheld OCT had the disadvantage of being very operator dependent and increasing the potential for breaking sterile technique.

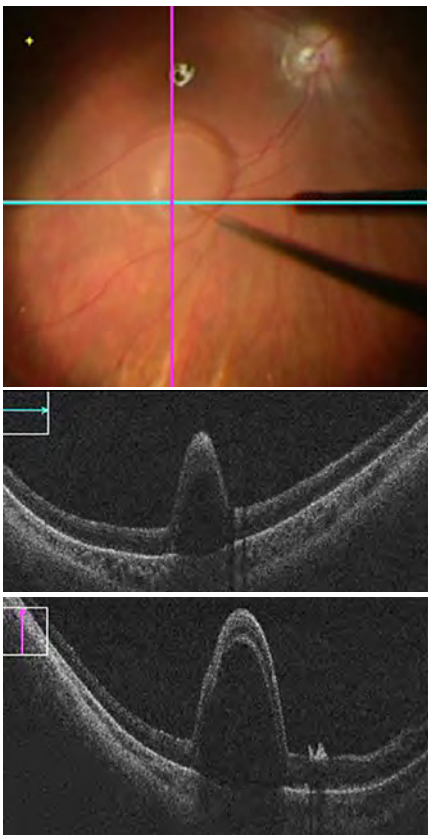
Built into the microscope. As the technology advanced, OCT was built into the microscope, said Dr. Ehlers. This allowed surgeons to more flexibly scan the area of interest and to do real-time OCT while operating, thereby speeding the workflow. "Once OCT was integrated into the microscope," said Dr. Lauer, "surgeons could do surgery while imaging, or pause surgery and image without having to change out devices. You could keep your hands on the instruments in the eye and control the OCT with a foot pedal." Alternatively, an assistant could control the OCT on a microscope panel.

FDA-approved systems. Although iOCT is not yet widely used in the United States, said Dr. Ehlers, 3 FDA-approved systems are available: the Haag-Streit iOCT, Zeiss Rescan 700, and Leica EnFocus. In addition, Leica also makes a handheld OCT system. All of these systems use spectral-domain OCT. He noted that some research systems use swept-source OCT.

iOCT Applications

Although researchers have not yet conducted randomized, controlled trials showing definitive benefits of iOCT, Dr. Ehlers said that it is having an impact in a variety of anterior and posterior segment surgeries.

Anterior segment surgeries. iOCT image acquisition is especially fast for anterior segment procedures, he said, as it typically takes 30 seconds or less



IN SURGERY. *Intraoperative optical coherence tomography during retinal gene therapy surgery using Zeiss Rescan 700. Vertical and horizontal line scans are depicted confirming viral vector delivery into the subretinal space.*

Andreas Lauer, MD, and Huber Vasconcelos, MD.

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **JUSTIS P. EHLERS, MD, ANDREAS K. LAUER, MD,** AND **ROBERT E. MACLAREN, MBCHB.**

to procure an image.

Procedures such as lamellar keratoplasty appear to particularly benefit from iOCT, said Dr. Lauer, by allowing the surgeon to image how the transplant is interfacing with the host cornea.

DMEK. One of the challenges of Descemet membrane endothelial keratoplasty (DMEK) is confirming the graft orientation, said Dr. Ehlers. In the United States, it's typically standard to S-stamp the tissue for feedback on graft orientation. "By using iOCT, however, surgeons have been able to eliminate tissue stamping, which may improve endothelial health, reduce cellular loss, and potentially improve graft survival."

DSAEK. Likewise, said Dr. Ehlers, iOCT can provide additional information during Descemet stripping automated endothelial keratoplasty (DSAEK) related to interface fluid and graft-host apposition, which is especially helpful when the cornea is hazy and the view is limited.

Corneal biopsy. "iOCT may also provide key information regarding depth information during anterior lamellar procedures, such as corneal biopsy or deep anterior lamellar keratoplasty," said Dr. Ehlers.

Posterior segment surgeries. "iOCT really comes into its own when you're working underneath the retina," said Robert E. MacLaren, MBChB, at the University of Oxford in the United Kingdom. "The macula is where you get the best images."

iOCT is not ideal for very peripheral retinal exams, but it is possible to get good images in about two-thirds of the retina, said Dr. Lauer. "It is helpful for conditions such as macular hole, epiretinal membrane or macular pucker, traction retinal detachment, and repair in patients with advanced diabetic retinopathy."

For most cases, Dr. Ehlers tends to do the initial part of the procedure and then reevaluate with iOCT to see if he has achieved his objectives. "This may require a 60- to 90-second pause to scan the whole macula or the area of interest," he said. However, the use of iOCT may actually decrease surgical time by confirming completion of surgical objectives earlier in the case.

Membrane peeling procedures. iOCT is helpful in visualizing the contour of the retina when you're peeling membrane, said Prof. MacLaren. Although visualizing agents can highlight these transparent membranes, said Dr. Lauer, there comes a moment of truth during surgery when you must decide "Did I remove enough or do I need to do more?"

"We often use the OCT to guide whether or not we've completed the membrane peeling," said Dr. Ehlers. "Because of the additional information that is provided by iOCT, it is rare that I need to re-stain, eliminating 1 step during surgery."

Choroidal-retinal biopsies. iOCT can be particularly helpful in identifying the optimal location to perform a choroidal-retinal biopsy, said Dr. Ehlers.

Argus implants. "At Cleveland Clinic, we have also found that iOCT can be utilized during Argus retinal implants to confirm and optimize the apposition of the electrode array against the retina," said Dr. Ehlers.

Gene therapy. Prof. MacLaren and Dr. Lauer consistently use iOCT for gene therapy. "For gene therapy to be effective, the material needs to be placed in the subretinal space," said Dr. Lauer, "but the operating microscope alone only provides an axial view of the retina." iOCT can help confirm that the targeted area has been reached. The technology is so useful, he said, that it is mandatory for some gene therapy research protocols.

Tips for Enhanced Use

As with any new technology, said Prof. MacLaren, there's always the chance for things to go wrong. "It's essential to get training so you know how to operate and troubleshoot when things don't work as planned." Other ways to ensure greater success include the following:

Start with simpler cases. "If you're a posterior segment surgeon," said Dr. Ehlers, "start with macular cases, such as epiretinal membranes, macular holes, or proliferative diabetic retinopathy with mild-to-moderate traction detachments."

Learn a step at a time. With different views, types of scan patterns, and image coloration, the instrumentation is powerful and can be overwhelming at first, said Dr. Lauer. As with the multiple features of your smartphone, it's difficult to master everything at once. "Learn 1 thing at a time in a stepwise fashion," he said. "For example, try to get the scan in the area of interest, bringing it into focus with the foot pedal. On a separate day, focus on rotating the image. Next learn how to magnify the image."

Keep at it. There certainly is a learning curve, added Dr. Ehlers. "But we have found that as users continue to apply the technology, their workflow improves and the utilization increases."

Groom an assistant. Having someone in your operating room who is comfortable with manipulating the OCT platform—whether a scrub nurse, circulating nurse, fellow, or resident—can make a big difference in ease of use, especially at first, said Dr. Ehlers.

"Knowledgeable and experienced assistants may even sometimes acquire images faster than the surgeon can," said Dr. Lauer.

Use it as a teaching tool. iOCT not only helps surgeons make more informed decisions, said Dr. Ehlers, "It can also help educate residents and fellows, elevating their clinical judgment by providing immediate feedback to compare with their gut impressions." In addition, said Dr. Lauer, having an OCT record of what was done during surgery can be helpful to study investigators and sponsors.

Barriers to Widespread Use

Prof. MacLaren first started using iOCT for gene therapy. "But once I began using it routinely, I found it quite useful for other cases as well. For example, if you're doing a retinal detachment operation, you can use the OCT to see how much subretinal fluid is in the macula." Still, barriers have prevented widespread use.

Cost. People do see the benefits, said Dr. Ehlers, but cost is keeping many from making the leap. "There is no way to recoup any of the cost because there isn't a code for reimbursement related to the technology, so it's a tough thing

to pull the trigger on." Clinicians need evidence that the modality results in better patient outcomes before they will consider the expense worthwhile, said Dr. Lauer.

"Cost is an issue," agreed Prof. MacLaren, "but it's not exorbitant when compared to other modern-day treatments in ophthalmology, especially if you're in the market for a new microscope. An iOCT microscope system will cost about $150,000-$350,000, depending on whether it is a stand-alone iOCT system or combined within the microscope. If you're doing an injection of Luxturna, that will cost $800,000. If the OCT scan tells you you've got the treatment in the right place, that seems to be a good investment."

Tracking. Tracking software exists in some of these platforms, said Dr. Ehlers, but these systems need improved accuracy and efficiency. Instrument tracking is currently not available but could be an important advancement to enhance surgeon feedback.

Software analysis. Also needed, said Dr. Ehlers, are software platforms that give more rapid, detailed surgeon feedback, for example, mapping out the residual epiretinal membrane or evaluating the amount of residual fluid between a corneal graft and a host cornea. This feedback could also be extremely helpful in the emerging field of subretinal or suprachoroidal drug delivery. "It would be helpful to be able to precisely measure the delivered therapeutic volume," he said.

Imaging quality. Although iOCT imaging quality is quite good, there is still room for improvement, said Dr. Lauer. Given the challenges of imaging in the surgical environment, image quality still lags behind those images obtained in clinical OCT systems, added Dr. Ehlers.

Other desirable enhancements. Prof. MacLaren would also like to see better integration with instruments. "Right now, when you bring an instrument to the retina, it creates a big artifact on the scan," he said. "It would be ideal to have instruments made of transparent material that do not create huge shadows on the retina when it is being scanned by the OCT.

"It would also be good to have the OCT image projected in the view in the assistant's eyepiece during surgery, which could help with training," he said.

Despite these shortcomings, Dr. Ehlers anticipates that iOCT will become a standard feature on microscopes over the next 5 years.

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Dr. Ehlers is the Norman C. and Donna L. Harbert Endowed Chair of Ophthalmic Research at the Cleveland Clinic in Cleveland. *Relevant financial disclosures: Alcon: C,S; Leica: C,P; Zeiss: C.*

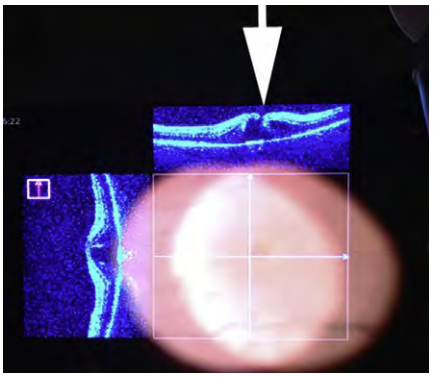
Dr. Lauer is a professor of ophthalmology at Casey Eye Institute at Oregon Health & Science University in Portland, Ore. *Relevant financial disclosures: None.*

Prof. MacLaren is a professor of ophthalmology at the University of Oxford in Oxford, United Kingdom. *Relevant financial disclosures: None.*

See disclosure key, page 8. **For full disclosures,** see this article at aao.org/eyenet.

PIONEER and DISCOVER Studies

Whether anterior or posterior segment surgery—what we're finding with iOCT across the board, said Dr. Ehlers, is that it adds information the surgeon wouldn't otherwise have—information that often changes the surgeon's perspective about the status of tissue.[1]



INTRAOP. *Example of iOCT overlay on a flat high-magnification contact lens.*

New or different information. "What we found consistently in PIONEER and DISCOVER—and replicated by other studies—is that a fairly high percentage of surgeons feel the extra information gained is helpful," said Dr. Ehlers. In the DISCOVER study, iOCT membrane peeling findings were discordant from the surgeon's initial impression in 19% of cases.[2]

Changing surgical practices. Studies have suggested that iOCT may change surgical decision-making in about 20% to 35% of cases, Dr. Ehlers said. "You might peel less; you might do a fluid-air exchange without a gas tamponade—things that could change how the patient does postoperatively."

In both the DISCOVER and PIONEER studies, iOCT impacted surgical decision-making and altered the surgical approach in a significant percentage of cases.[2-4]

"Having that extra information is something that has real potential to enhance the value of what we're bringing to patients in terms of precision care and individualized surgical treatments," said Dr. Ehlers.

Clinical trials still needed. "We are working on designing prospective, controlled, multicenter iOCT trials," said Dr. Ehlers. "But it is difficult to control various aspects of surgical procedures that can influence the results of surgical clinical trials." Invariably, there is individual variation in practices, added Prof. MacLaren.

It will take large numbers of patients to confirm the clinical benefits of iOCT, said Dr. Lauer. He suggested that developing a consortium to evaluate iOCT may be one method for gathering more data more quickly.

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Diagnosis and Management of Giant Retinal Tear

Giant retinal tears (GRTs) are full-thickness circumferential retinal tears that involve more than 3 clock hours (90 degrees) of the peripheral retina and develop in association with a posterior vitreous detachment. The reported incidence of GRT is about 0.09 per 100,000 persons. This condition is more common in males (72%), occurring at an average age of 42 years. GRTs are bilateral in 12.8% of patients over time,[1,2] although they rarely develop simultaneously. GRTs account for approximately 1.5% of rhegmatogenous retinal detachments (RD), and surgical management of an RD associated with a GRT may be challenging.

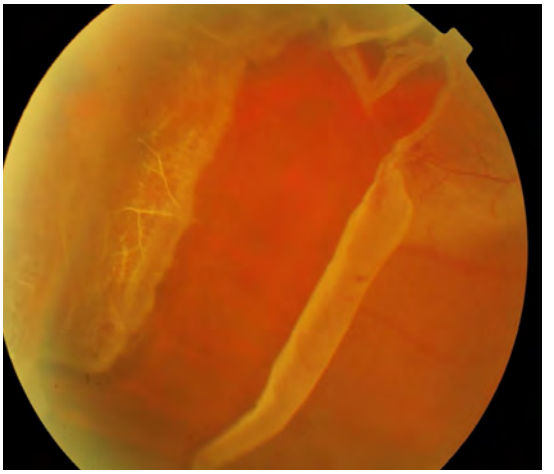
Pathogenesis

GRTs are caused by vitreous traction on the peripheral retina in the area of the vitreous base in association with peripheral vitreous condensation and liquefaction of the central vitreous. When subsequent transvitreal contraction of the cortical gel occurs, the retina tears along the vitreous base in a zipper fashion.[3]

In some cases, a GRT may result from the coalescence of multiple horseshoe-shaped tears that form along the posterior vitreous base during vitreous liquefaction and separation. With a GRT, the vitreous gel remains adherent to the anterior flap of the torn retina; this feature differentiates it from a retinal dialysis, in which the vitreous gel is attached to the posterior flap of the dialysis.[2] As such, the posterior flap of the GRT is freely mobile and has a tendency to fold over posteriorly.

Risk Factors

Risk factors for GRT may be ocular or systemic. Ocular risk factors include high myopia and closed globe injury, while systemic risk factors include young age, collagen vascular disorders (e.g., Stickler, Wagner, Marfan, and Ehlers-Danlos syndromes). However, the majority of GRTs (54%) are idiopathic.[1]



GIANT RETINAL TEAR. *GRT associated with macula-off retinal detachment in a 39-year-old man with high myopia (–10 D).*

Management Tips for GRT

Without RD. In the absence of an associated RD, demarcation of the GRT with laser photocoagulation with or without adjunctive cryotherapy may be considered. One should aim to apply at least 3 concentric rows of confluent white retinal burns along the edges of the GRT. It is important to apply the laser all the way to the ora serrata to reduce the risk of an RD. It is critical to thoroughly check the remaining retina to ensure there are no other breaks.

With associated RD. If an RD is present but the GRT is not inverted, a scleral buckle with cryotherapy alone may be an appropriate treatment and obviate the need for vitreous surgery. However, if the GRT is folded over on itself, management of the associated RD involves vitreous surgery.

Perfluorocarbon liquids. In such cases, injection of a perfluorocarbon liquid (PFCL) is used to unfold, flatten, and immobilize the posterior retina. A thorough shaving of vitreous around the GRT is crucial in relieving traction and thus preventing subsequent retinal redetachment.

Intraoperative posterior retinal slippage with associated posterior retinal folds may occur during the air-fluid exchange and removal of the PFCL. Several techniques have been described to reduce slippage, including meticulous drying of the retinal pigment epithelium along the edges of the GRT or a direct perfluorocarbon-silicone

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exchange. In order to optimize the likelihood of anatomic success, long-acting gas tamponade (such as C_3F_8) is often employed. However, adherence to face-down postoperative positioning may be difficult for some patients; in these cases, silicone oil tamponade may be used instead.

To buckle or not? In eyes undergoing vitreous surgery for GRT-associated RD, the value of adding a scleral buckle remains controversial. Some surgeons feel that its use is associated with an increased risk of retinal slippage during the air-fluid exchange. However, others believe that buckling is an essential part of the surgical management, as it helps to relieve the traction at the edges of the GRT and provides support for the rest of the vitreous base. When proliferative vitreoretinopathy (PVR) is present, a combined approach involving vitrectomy as well as a scleral buckle is commonly employed.[4]

Phakic patients. With the availability of improved vitreoretinal surgical instrumentation, such as curved and illuminated endolaser probes and wide-angle viewing systems that allow surgeons to better visualize the operative field, phakic lens-sparing surgery has become more common. Also, the use of chandelier illumination aids scleral depression and clearing of the anterior vitreous without traumatizing the lens.

Sparing the lens enables more accurate intraocular lens (IOL) calculations for subsequent cataract surgery compared with the inaccurate biometry that is common when an RD is present. The main disadvantage of lens-sparing surgery is the increased technical difficulty of clearing the anterior vitreous without damaging the lens.

However, in the presence of a visually significant cataract that interferes with retinal repair, cataract removal is necessary. Concurrent phacoemulsification may be considered or, alternatively, pars plana lensectomy that leaves the peripheral anterior capsule intact for subsequent placement of a sulcus IOL. Another option is to remove the capsule and plan for secondary IOL placement at a later date. An IOL is not usually inserted at the same time as retinal repair.

Prognosis

Risk factors for retinal redetachment include traction at edges of the GRT; missed breaks; development of PVR; and, in highly myopic eyes, macular hole formation. PVR may occur in 40% to 50% of GRT-associated detachments and is seen more commonly in traumatic and chronic RDs.[5]

Management of Fellow Eye Without a GRT

Although the fellow eye is at risk for developing a GRT, prophylactic treatment remains controversial. Higher-risk fellow eyes include those with high myopia, Wagner or Stickler syndrome, and progressively increasing areas of white-without-pressure (WWOP) with a sharp posterior margin and increased vitreous condensation. (WWOP refers to areas of the retina that appear whitened even without the pressure of scleral indentation; this condition is often associated with retinal or vitreous degeneration.)

There is no consensus on the need for prophylaxis, type of treatment, and area of treatment (ora/equator, lattice degeneration/areas of WWOP, or 360 degrees). Some authors advocate prophylactic 360-degree cryotherapy posterior to the ora serrata in the fellow eye of persons with Stickler syndrome,[6] while others have suggested prophylactic buckling along with cryopexy.[7] Prophylactic 360-degree laser photocoagulation can also be considered, especially in eyes with multiple risk factors.

Conclusion

A GRT is a potentially blinding condition, but early treatment can improve the visual prognosis. Modern vitrectomy tools and techniques, including wide-angle viewing systems, chandelier illumination, and PFCLs, have increased the success rates of GRT-associated RD repair.

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Dr. Phua is an ophthalmology resident in the Singapore National Eye Center (SNEC). **Dr. Ting** is an associate consultant at SNEC and assistant professor at Duke-National University Singapore (Duke-NUS) Medical School. **Dr. Wong** is a senior retinal surgeon at SNEC and was also the immediate past head of surgical retina department and an adjunct associate professor at Duke-NUS Medical School. *Financial disclosures: None.*

When prescribing a steroid to treat inflammation and pain associated with ocular surgery and for the treatment of endogenous anterior uveitis,

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Study Design: Two randomized, double-masked, placebo-controlled trials evaluated the efficacy of DUREZOL® Emulsion QID (n=107) versus placebo QID (n=220) in patients with an anterior chamber cell count ≥11 one day after cataract surgery; $P<0.05$.[2]

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in nearly 2x more patients at days 3, 8, and 15[2]

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Evaluation of Pain: Symptoms of pain and discomfort were collected at each visit and graded 0 to 100 according to a visual analogue scale that used a mark on a 100-mm line (with anchor points of 0=absent and 100=maximal pain or discomfort).[4,5]

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INDICATIONS AND USAGE
DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a topical corticosteroid that is indicated for:
- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

Dosage and Administration
- For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
- For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

IMPORTANT SAFETY INFORMATION

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

Warnings and Precautions
- *Intraocular pressure (IOP) increase* – Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- *Cataracts* – Use of corticosteroids may result in posterior subcapsular cataract formation.
- *Delayed healing* – The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- *Bacterial infections* – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- *Viral infections* – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- *Fungal infections* – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- *Contact lens wear* – DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Most Common Adverse Reactions
- In postoperative ocular inflammation and pain studies, ocular adverse reactions occurring in 5-15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.
- In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion, please see Brief Summary of Prescribing Information on adjacent page.

References: 1. Data on file. IMS SMART MVP solutions. Novartis Pharmaceuticals Corp; Oct 2016. **2.** Durezol [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; April 2017. **3.** Fingertip Formulary, January 2018 (estimate derived from information used under license from Fingertip Formulary, LLC, which expressly reserves all rights, including rights of copying, distribution and republication). **4.** Data on file. Study ST-601A-002a. Novartis Pharmaceuticals Corp; 2007. **5.** Data on file. Study ST-601A-002b. Novartis Pharmaceuticals Corp; 2007.

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DUREZOL® (difluprednate ophthalmic emulsion) 0.05%
Initial U.S. Approval: 2008

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

1 INDICATIONS AND USAGE

1.1 Ocular Surgery

DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.

1.2 Endogenous Anterior Uveitis

DUREZOL is also indicated for the treatment of endogenous anterior uveitis.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Intraocular pressure (IOP) Increase

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

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated.

5.5 Viral Infections

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

5.6 Fungal Infections

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

5.7 Topical Ophthalmic Use Only

DUREZOL is not indicated for intraocular administration.

5.8 Contact Lens Wear

DUREZOL should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL. The preservative in DUREZOL may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL.

6 ADVERSE REACTIONS

The following serious reactions are found elsewhere in the labeling:

- Elevated IOP *[see Warnings and Precautions (5.1)]*
- Posterior subcapsular cataract formation *[see Warnings and Precautions (5.2)]*
- Secondary ocular infection *[see Warnings and Precautions (5.4)]*
- Perforation of the globe *[see Warnings and Precautions (5.3)]*

6.1 Ocular Surgery

Ocular adverse reactions occurring in 5% to 15% of subjects in clinical studies with DUREZOL included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1% to 5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in less than 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

6.2 Endogenous Anterior Uveitis

A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL. The most common adverse reactions of those exposed to DUREZOL occurring in 5% to 10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2% to 5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects

Pregnancy Category C

Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal anomalies) when administered subcutaneously to rabbits during organogenesis at a dose of 1-10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL, since DUREZOL is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

8.3 Nursing Mothers

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

8.4 Pediatric Use

DUREZOL was evaluated in a 3-month, multicenter, double-masked trial in 79 pediatric patients (39 DUREZOL; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL to prednisolone acetate ophthalmic suspension, 1%.

8.5 Geriatric Use

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

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T2017-52
April 2017

Foggy With a Chance of Hemorrhage

Tatiana Ivanov,* a 79-year-old Albanian woman now living in New York City, grimaced and held her hand over her right eye. She reported that the vision in that eye had become blurry 4 days earlier. Two days after the onset of blurred vision, she began to experience severe pulsating eye pain and worsening vision. Now, she said that she could see only "fog" with her right eye.

Ms. Ivanov described several episodes of self-limited painless vision loss in the right eye that had occurred over the past year. Each of these lasted a few days before her vision returned to normal. Apart from these episodes, she had enjoyed excellent vision in her right eye since undergoing cataract surgery 5 years ago.

Emergency Department Findings

Ms. Ivanov was first seen in the ED, where her visual acuity was recorded as light perception in the right eye and 20/25 in the left eye. Intraocular pressure (IOP) was 70 mm Hg in the right eye and 12 mm Hg in the left eye. Slit-lamp examination showed profound microcystic edema of the right cornea, limiting visualization of intraocular structures. B-scan ultrasonography revealed vitreous hemorrhage.

Intravenous acetazolamide and serial IOP-lowering drops were administered, and her IOP improved to 26 mm Hg prior to discharge from the ED.

We Get a Look

The following day, Ms. Ivanov presented at our office feeling much better; her eye pain had resolved, and IOP was 12 mm Hg in the right eye. Additional history revealed that she had systemic hypertension, dyslipidemia treated with statins, and exfoliation syndrome (XFS).

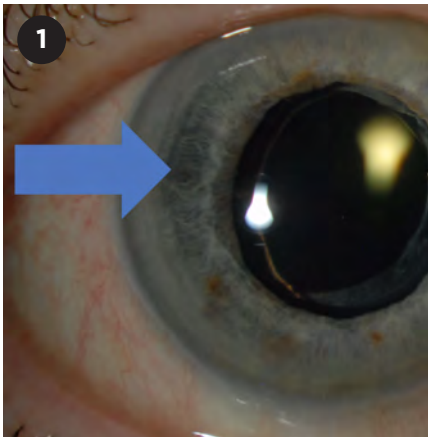
Gonioscopy showed an open angle in the right eye with hyphema inferiorly. We saw no neovascularization of the angle. The anterior chamber was filled with 4+ cells; although both pigmented and nonpigmented types were present, the pigmented cells were more numerous. A well-centered single-piece posterior chamber intraocular lens (IOL) was noted.

Differential Diagnosis

The profusion of pigmented cells in the anterior chamber coupled with the vitreous hemorrhage suggested that intraocular bleeding was the most likely cause of the marked IOP elevation. Our differential diagnosis included hemolytic glaucoma and ghost cell glaucoma, both of which can develop following vitreous hemorrhage.

In hemolytic glaucoma, hemoglobin-laden macrophages produce obstruction of the trabecular meshwork, and red cells predominate in the anterior chamber. In ghost cell glaucoma, degenerated red blood cells that have lost their intracellular hemoglobin cause the outflow obstruction, and small, khaki-colored "ghost cells" are noted in the anterior chamber. Vitreous hemorrhage is usually present for 1 to 3 months before red blood cells degenerate into ghost cells. Given the sudden onset of Ms. Ivanov's blurry vision 4 days prior to presentation and the predominance of pigmented cells in the anterior chamber, hemolytic glaucoma was the most likely explanation for the elevated IOP.

However, the etiology of the vitreous hemorrhage remained unclear. Although Ms. Ivanov had a history of hypertension, there were no signs of hypertensive retinopathy in the fellow eye. Our



IRIS TRANSILLUMINATION. *Slit-lamp exam 1 month after presentation reveals crescent-shaped iris transillumination defects nasally and temporally (arrow). We also observed pseudophacodonesis.*

Sarah H. Van Tassel, MD

BY **RICHMOND WOODWARD, BA, ABDALLAH MAHROUS, MD, MRINALI P. GUPTA, MD,** AND **SARAH H. VAN TASSEL, MD.** EDITED BY STEVEN J. GEDDE, MD.

working diagnoses were acute hemorrhagic posterior vitreous detachment or retinal vein occlusion, and consultation with a retina specialist was arranged. In the meantime, IOP-lowering therapy was continued.

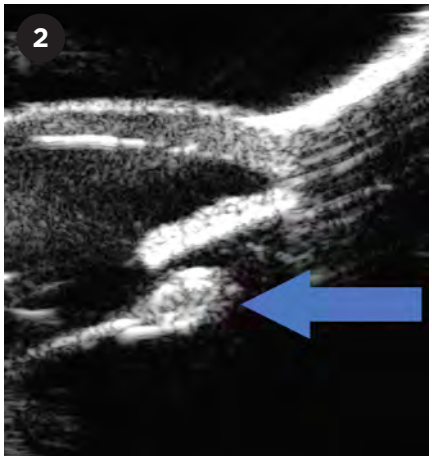
Next Steps

Retina consult. Ms. Ivanov saw the retina specialist 8 days after presentation. The vision in her right eye had improved to 20/50, and the IOP was 12 mm Hg. The anterior chamber was still filled with pigmented cells, and the vitreous hemorrhage was clearing. Ms. Ivanov's daughter, who accompanied her to the appointment, recalled that her mother's blood pressure had been very high in the weeks before the severe eye pain started. However, Ms. Ivanov's retinal examination and fluorescein angiography showed no evidence of retinal vascular occlusion to implicate hypertension as the etiology of the bleeding. The hyphema was followed to resolution, and the vision in the right eye improved to 20/25.

Optic nerve head exam. Once the vitreous hemorrhage had cleared, we could examine the optic nerve head. In the right eye, we found a vertical cup-to-disc ratio of 0.6 with thinning of the inferior neuroretinal rim; in the left eye, we observed a cup-to-disc ratio of 0.3. Optical coherence tomography (OCT) demonstrated intact and symmetric retinal nerve fiber layer thickness and inferior ganglion cell loss in the right eye. Automated perimetry was performed reliably in both eyes. Several superonasal pixels were present in the right eye, raising concern for an early nasal step. The left eye testing was full.

New Findings

About 1 month after the initial presentation, Ms. Ivanov returned for follow-up, reporting another episode of vision loss—which had since resolved—in the previous week. Slit-lamp exam now showed crescentic, haptic-shaped iris transillumination defects nasally and temporally (Fig. 1) and pseudophacodonesis. Ultrasound biomicroscopy (UBM) revealed a normal iris configuration, a single-piece IOL in the capsular bag, and a Soemmering ring (Fig. 2). No vitreous hemorrhage was noted.



UBM. *Ultrasound biomicroscopy 4 weeks after initial presentation shows single-piece IOL in the capsular bag and a Soemmering ring (arrow). There was suspicion that a haptic was abutting the ciliary body nasally, but it was poorly visualized by UBM.*

We strongly suspected uveitis-glaucoma-hyphema (UGH) syndrome at this point. We discussed the options of ongoing observation versus surgery to remove the IOL. The decision was made to monitor the condition, with consideration of surgery if significant or recurrent hemorrhages or IOP elevation were noted. IOP-lowering medications and topical steroids were continued.

Making the Diagnosis

Eight weeks after initial presentation, Ms. Ivanov returned acutely for decreased vision. In the right eye, her visual acuity was hand motions, and IOP was 32 mm Hg despite good compliance with IOP-lowering drops. A new microhyphema and diffuse vitreous hemorrhage were present, and the pseudophacodonesis appeared more dramatic than at the last examination, confirming the diagnosis of UGH syndrome in the setting of XFS and late zonular weakness.

Discussion

UGH syndrome was initially described in 1978 as a complication of first-generation anterior chamber IOLs that caused chafing of intraocular structures.[1] It is now known that virtually any IOL can cause UGH syndrome, including modern anterior chamber IOLs, sulcus IOLs (both 3-piece and single-piece IOLs, which may be inadvertently or purposely placed in the ciliary sulcus[2]), and IOLs placed in the capsular bag.[3,4]

Blood-aqueous barrier compromise due to the chafing results in the classic triad of uveitis, glaucoma, and hyphema. IOP elevation can be caused by inflammation and resultant scarring of the trabecular meshwork, by pigment and hyphema clogging the meshwork, and by direct injury to the aqueous drainage complex. Iris transillumination defects, secondary neovascularization of the iris, and cystoid macular edema may also occur. The term "UGH Plus syndrome" has been used to describe the condition of patients such Ms. Ivanov, who, in addition, have vitreous hemorrhage.[5]

In-the-bag UGH. Single-piece IOLs in the capsular bag are a rare but increasing cause of UGH syndrome.[4] Zhang et al. reported a patient with XFS and UGH syndrome 3 years after uneventful placement of a single-piece IOL in the capsular bag. They posit that the haptic-capsule complex chafed the posterior iris in the setting of subclinical pseudophacodonesis.[4]

Bryant et al. observed extensive fibrosis (Soemmering ring) around the haptics of the single-piece IOL in the capsular bag in a patient with UGH syndrome. They suspected that the fibrosis caused the IOL to tilt out of the iris plane, leading to haptic-iris and haptic–ciliary body chafing.[3]

Single-piece IOLs are now the most commonly implanted lenses in the United States. Given the aging of the U.S. population, ophthalmologists may encounter a growing number of cases of in-the-bag UGH syndrome in the future.

Treatment. Topical therapy with steroids and IOP-lowering medication, with or without cycloplegia, is the first-line treatment. Photocoagulation to ablate leaking vessels, intravitreal anti–vascular endothelial growth factor medications, and placement of a capsular tension ring to adjust IOL positioning have all been described as therapies

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for UGH syndrome.[5] However, removal of the IOL is often required, as in our patient's case. In a series of 109 eyes at a tertiary referral center, UGH syndrome was among the most common reasons for IOL exchange, accounting for 11.9% of cases.[6]

Key considerations. The presence of seemingly spontaneous hyphema along with elevated IOP and inflammation should prompt clinicians to consider UGH syndrome, even if the patient has a single-piece IOL in the capsular bag. This consideration is particularly important in eyes that are susceptible to zonular weakness, such as those with XFS or a history of ocular trauma. Careful slit-lamp examination, gonioscopy, and UBM are important tools in making the diagnosis of UGH syndrome.

Our Patient

Ms. Ivanov underwent pars plana vitrectomy, IOL removal, and placement of a scleral-sutured Akreos AO60 IOL. At 4 months following surgery, best-corrected visual acuity was 20/25 in the right eye, and IOP was in the midteens on a prostaglandin analogue and fixed-dose combination drops. Serial OCT and visual field testing were stable. No further episodes of decreased vision were reported.

* Patient name is fictitious.

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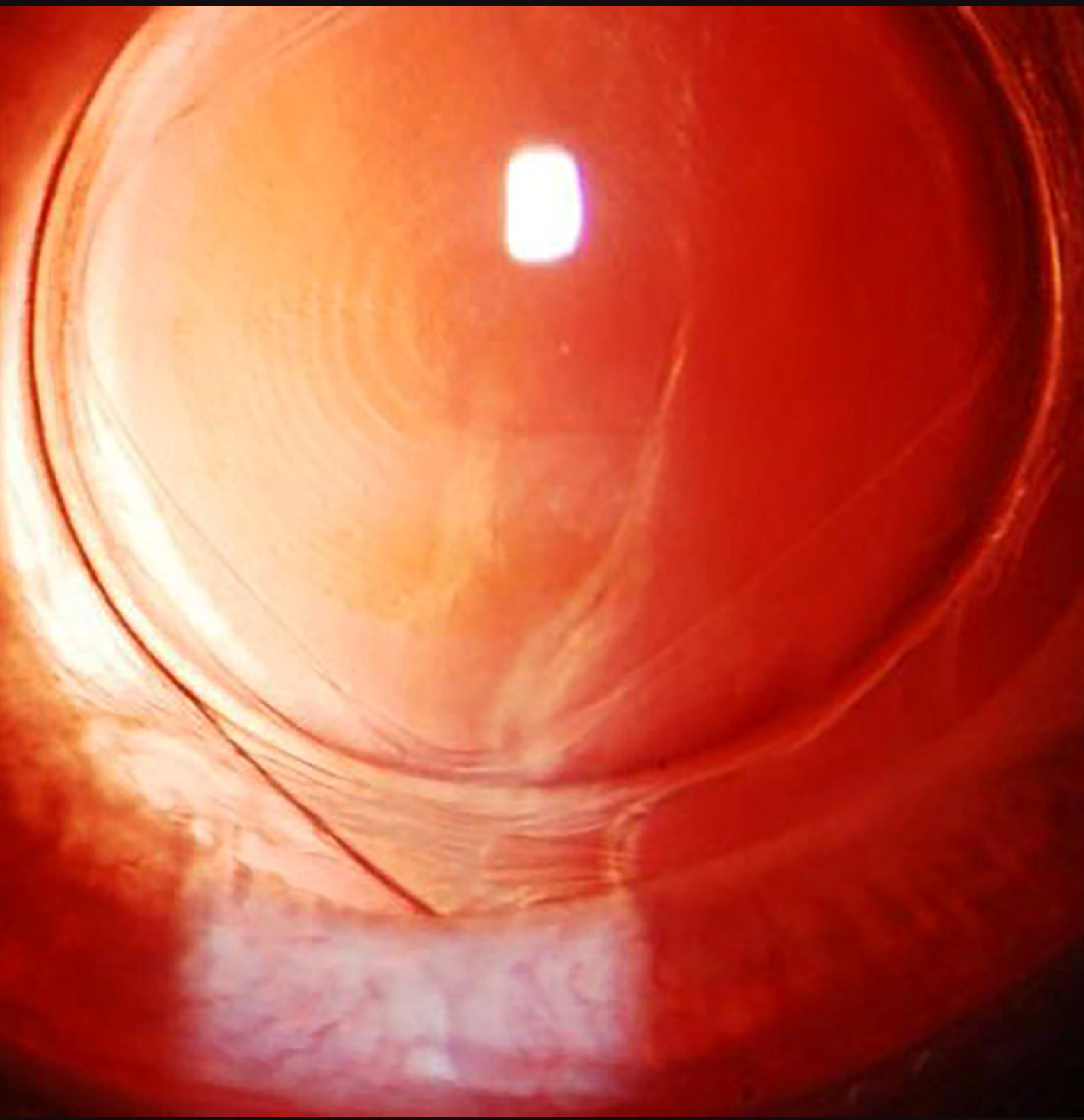


Cataract Innovations

Intracameral antibiotics, refractive indexing, and drops that "dissolve" cataracts: A look at 3 disruptive technologies poised to reshape the field.

By Annie Stuart, Contributing Writer

ALTHOUGH CATARACT SURGERY is already one of the safest, most effective surgeries worldwide, its evolution continues. Three technologies—1 now in use and 2 in development—may go a long way toward transforming the field, whether by reducing the need for postoperative drops, revolutionizing the approach to intraocular lens (IOL) adjustment, or allowing the clinician to circumvent cataract surgery altogether.

Moving Toward Drop-Free Surgery

Around the turn of the millennium, the incidence of endophthalmitis in the United States was reported to range from 1 in 300 to 1 in 1,000, said Neal H. Shorstein, MD, at the Kaiser Permanente Medical Center in Walnut Creek, California. "Today, it's more typical to see rates of 1 in 5,000 to 1 in 10,000," he said.

What's behind this decrease? "One reason is that surgeons are more aware of wound construction and management," Dr. Shorstein said. Another contributing factor may be the increasing adoption of intracameral antibiotics (IA)—that is, direct delivery to the inside of the eye right after cataract surgery.

Making inroads. Although IA is a controversial practice, it is gaining momentum, based in part on the following.

Drug delivery. With IA, you inject directly into the anterior chamber, where you want the drug to stay for some time after surgery, said Dr. Shorstein. "Depending upon the agent and how much you are injecting, the concentrations in the eye are on the order of about 1,000 to 3,000 micrograms per milliliter—high enough to overcome even resistant strains of coagulase-negative *Staphylococcus*, one of the most common causative organisms," he said. "With topical drops applied to the surface of the eye, however, the concentration of antibiotic in the anterior chamber is too low to overcome organisms with higher resistance."

Patient perspective. In general, IA is a financial win for patients because they will need fewer medications, said Michael Greenwood, MD, at Vance Thompson Vision in Fargo, North Dakota.

In addition, IA can circumvent problems with adherence. "Patients often have difficulty instilling eyedrops" and may inadvertently scratch their conjunctiva or cornea with the eyedrop container, Dr. Shorstein said. "Or they may never purchase their drops, fail to instill them in proper intervals, or simply stop using them (prematurely)." A quick, one-time injection by the surgeon circumvents these problems.

Lingering concerns. Those who are uneasy with the widespread adoption of IA cite the need for more level 1 evidence from randomized clinical trials (see "IA Research Notes"). Other barriers to its use include the following.

No FDA approval. U.S. surgeons do not have an FDA-approved IA agent available. Instead, ophthalmologists may have their hospital compound the antibiotic or use compounding pharmacies such as ImprimisRx, Leiters, and Avella Specialty Pharmacy, which are FDA-registered 503B outsourcing facilities, said Dr. Greenwood.

And because the surgery center generally bears

Photo courtesy of Perfect Lens

the cost of procuring the product, this adds another barrier in terms of increased operating costs.

Potential toxicity. Surgeons may also worry about compounding errors, which can lead to insufficient antibiotic strength or toxicity, said Dr. Greenwood. For example, a primary risk of cefuroxime, said Dr. Shorstein, is temporary or permanent macular toxicity. In rabbit studies and in human tissue culture, moxifloxacin has displayed a risk of corneal endothelial toxicity. Another potentially blinding complication is hemorrhagic occlusive retinal vasculitis (HORV), which has been linked to the use of vancomycin (see "Questions about half-life").

"Any time you're using a compounding pharmacy, you want to make sure it is following federal regulations," Dr. Greenwood said. Similarly, if your clinic or local hospital is doing the compounding, the process must be painstakingly accurate and in accordance with all regulations, he said.

Questions about half-life. The research in the literature is slightly divergent on the exact half-life of drugs in the anterior chamber, said Dr. Shorstein. "For cefuroxime and moxifloxacin, the concentration is above typical organisms' MIC90 for about 4 to 6 hours. For vancomycin, it's longer." However, because of the risk of HORV, he noted, the FDA and the American Society of Cataract and Refractive Surgery (ASCRS) strongly advise against the routine injection of vancomycin for the prophylaxis of endophthalmitis.

Intracameral modifications. Many surgeons who use IA also combine it with another medication. In addition, some surgeons use IA without adding topical antibiotic drops, Dr. Shorstein said (see "Going drop free," below).

Dr. Greenwood places Dex-Moxi-Ketor (ImprimisRx) into the anterior chamber after surgery. (Dex-Moxi-Ketor is short for dexamethasone, moxifloxacin, and ketorolac, which are steroid, antibiotic, and nonsteroidal anti-inflammatory medications, respectively.) He and his colleagues[1] found that "intravitreal injection of an antibiotic and a steroid does not create significant intraocular pressure (IOP) spikes following cataract surgery in patients with glaucoma," he said.

Dr. Greenwood's approach is not entirely drop free, however. "For a month, patients take 1 drop once a day of a combination of prednisolone acetate, gatifloxacin, and bromfenac, a combination medication that is also from ImprimisRx," he said. By doing so, he explained, he's eliminated about 80 drops from his cataract patients' postsurgical regimen.

Going drop free. In contrast, before cataract surgery, Dr. Shorstein's patients receive only a dilating drop. After cataract surgery, he has patients apply no drops, pointing out that large studies have underscored the lower infection rates using IA alone (see "IA Research Notes").

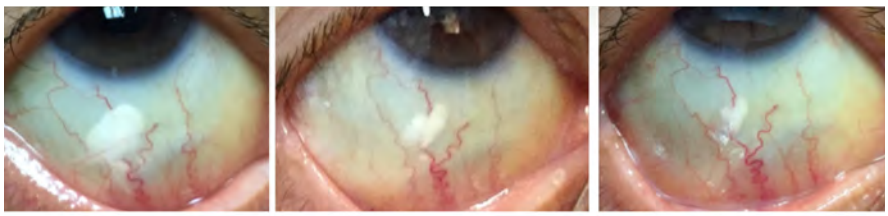
ANTIBIOTICS. *Intracameral delivery of antibiotics immediately after cataract surgery. The procedure emerged in 2005 with the publication of a European study.*

"Our study[2] showed that an injection of triamcinolone, delivered subconjunctivally, is just as effective in preventing postoperative macular edema as topical postop steroid drops," said Dr. Shorstein, who does prescribe topical steroid drops postoperatively for patients with glaucoma and a compromised optic nerve. "This long-acting steroid injection, along with the intracameral antibiotic injection, make up the drop-free technique."

Other ways to lower risk. A variety of techniques further lower the risk of endophthalmitis, said Dr. Greenwood. This includes a good Betadine prep prior to surgery, sterile techniques during surgery, and placement of a Betadine solution on the eye at the end of surgery.

In addition, some studies have concluded that, because IOP can dip soon after surgery, it's advantageous to perform stromal hydration at the end of the surgery. "Leaving the eye adequately pressurized with a slightly increased IOP helps seal the corneal flaps together and ensure wound closure following the procedure," said Dr. Shorstein.

After surgery, he also instructs his patients to avoid touching or rubbing their eyes for 24 to 48 hours, and to not apply any artificial tears. "Although there's no hard evidence, it's my belief that the less patients manipulate their eyes, the lower the risk of endophthalmitis," he said.



NO MORE DROPS? *From left: One day, 4 weeks, and 6 weeks following a subconjunctival injection of 3 mg of triamcinolone acetonide. Some research indicates that this prevents postoperative macular edema as effectively as postop steroid drops do.*

Neal H. Shorstein, MD

Rethinking Refractive Error Correction

Refractive index shaping—also known as refractive indexing—uses a minimally invasive, ultrafast femtosecond laser to change the refractive index ab interno of an IOL without measurably changing its shape, said Scott M. MacRae, MD, at the University of Rochester in New York. "The laser has about 100 times less pulse energy" than commercial femtosecond lasers now in use, he said.

Procedure basics. Before the laser adjustment, the subject receives topical anesthesia and drops to dilate pupils, said Liliana Werner, MD, PhD, at the University of Utah in Salt Lake City. The subject's eye is aligned and docked to the femtosecond laser system, and appropriate laser treatment is then applied.

Research. Currently, 2 companies are evaluating the technology: Clerio Vision is working with researchers at the University of Rochester, and Perfect Lens is collaborating with researchers at the University of Utah.

"We are experimenting with different types of IOL materials to observe how they react and to determine the best energy levels to use," said Dr. MacRae. "Although certain materials do change more than others, the response is very uniform for each type of material." He added, "We have tested a variety of commercially available lenses and some noncommercial materials, and they have a predictable response to refractive indexing."

The technology has not been tested with silicone or PMMA lenses, but it works well with commercially available hydrophobic and hydrophilic acrylic lenses, said Dr. Werner.

One option would be to use these types of monofocal lenses with the initial power selected for each eye, according to current standards of care, with the idea that they could be modified later. Another approach would involve developing a material that is very responsive to refractive indexing, which could provide even more control and flexibility, said Dr. MacRae.

Multiple adjustments possible? This technology opens up the possibility of responding to refractive error changes that occur over time, said Dr. MacRae. Many adjustments may be possible, said Dr. Werner, because each treatment is applied to only a very thin layer within the IOL. "Ongoing studies are assessing this, as well as the amount of power change that can be obtained before the quality of the IOL optic decreases," she said.

Potential benefits. The laser treatment can be done in a noninvasive manner under topical anesthesia, and it is very fast, said Dr. Werner. "In our rabbit studies, the treatment took 23 seconds for a change of +3.6 D." Other potential advantages include the following:

Precision. The precision obtained with the power adjustment by the femtosecond laser is within 0.1 D of the target and is very consistent, said Dr. Werner.

Address a wide range of refractive errors. "We know we can treat ± 4 diopters, and potentially quite a bit more, depending upon the type of [IOL] material," said Dr. MacRae. He added that refractive indexing can be used to treat residual myopia, hyperopia, astigmatism, and higher-order aberrations, as well as to create diffractive bifocals, trifocals, and other patterns.

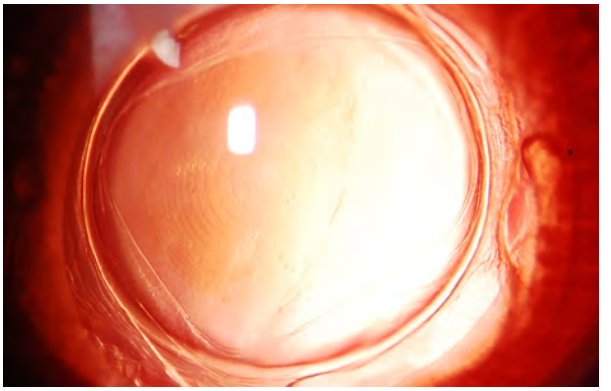
Flexibility. Analyses of the optical quality through modulation transfer function (MTF) measurements of the lenses[3] show that a monofocal lens can be changed into a multifocal lens, with resulting MTF values for far and near foci similar to commercially available multifocal lenses, said Dr. Werner. (The MTF of an IOL is a measurement of its ability to reproduce the image of an object.)

"That same lens can be turned back into a monofocal lens, and the final MTF obtained is very close to the original MTF of the initial monofocal lens. This means that all of those changes can be performed without any significant decrease in the optical quality of the original lens."

Negligible toxicity. Standard tests have been performed on modified IOLs, and no leachables were found, said Dr. Werner. Also, in vivo studies performed in rabbits showed no inflammatory reaction or signs of toxicity up to 6 months postoperatively. Anti-inflammatory treatment was not applied to the rabbit eyes after laser treatment, she added.[4]

Candidates. Who might eventually benefit from refractive indexing? One example is children with congenital cataracts, whose refractive error changes over time as the eye develops. Other potential recipients include those patients who have residual refractive errors after cataract surgery, who would like to have their monofocal IOL converted to a multifocal IOL, or who cannot adapt to their current multifocal IOL, said Dr. Werner.

Next up: results in humans. Dr. Werner expects results from the first human trial shortly. And more human data on refractive indexing will become available over the next 1-2 years, said Dr. MacRae. "Big issues that need



REFRACTIVE INDEXING. *This image is of a rabbit eye implanted with a commercially available IOL, 5 hours after refractive index shaping. What looks like a multifocal pattern—visible individual zones in the IOL—is a refractive change.*

Courtesy of Perfect Lens

to be fully worked out are reproducibility, long-term biocompatibility, and optical performance. All the work thus far has been done in animals or on the bench. It's exciting, but we need to make the airplane fly."

Other uses for refractive index shaping. Refractive index shaping also shows promise in 2 additional areas, Dr. MacRae said.

Modifying contacts. "Making diffractive and refractive index changes internally, rather than on the outside of the lens, means that [the clinician] could create a much thinner lens for high myopes or hyperopes, thus improving the oxygen permeability and comfort level," he said. "You could also create a diffractive multifocal optic internally in the contact lens." Doing so isn't possible with the current generation of multifocal contact lenses, which essentially are designed as "refractive" multifocals, he said.

Treating corneas. If it becomes possible to use refractive index shaping on the cornea, that would be a game changer, said Dr. MacRae, as it does not significantly affect corneal nerves or provoke much in the way of a wound healing response. "If refractive indexing can treat higher degrees of refractive error, it has the potential to revolutionize the field," he said. "And if the technology could be made portable, it could go a long way toward attacking the problem of refractive error."

In addition, any cornea treatments can be placed in layers so that multiple treatments could be done sequentially, as the refraction changes. "You can put a treatment in and go 20 microns deeper and then repeat the treatment, if needed," he said. "For example, if you treat a 16-year-old with a diopter of myopia, you can re-treat at age 22 or 23, if she gains another diopter of myopia."

Dr. MacRae explained that the energy levels used in refractive indexing are so low as to be nondisruptive. "We are micromachining the cornea and causing densification of the collagen fiber spacing, based on our histopathologic studies." Animal models have demonstrated that this technology does work and is stable and persistent for at least 2 years, he said. With regard to impact upon keratocytes, the animal studies have found minimal, localized keratocyte death only within the laser focal zone.[5]

Reducing Cataracts With an Eye Drop

In 2015, a team of researchers at the University of California, San Diego was reviewing the genetic makeup of 2 families with congenital cataracts. What they found was like so many serendipitous discoveries in medicine: Each family member with cataracts had a mutation in the lanosterol synthase gene (*LSS*), which had no previously known association with cataracts. This mutation stopped production of lanosterol, a naturally occurring steroid. "That led us to the idea that lanosterol was, in fact, important for keeping lens proteins from aggregating and producing cataracts," said Kang Zhang, MD, PhD, who heads the research team.

Lanosterol. "We conducted studies using a naturally occurring age-related cataract in rabbits and dogs," said Dr. Zhang.[6] "We took the rabbits' cataractous lenses out and incubated them in test tubes with lanosterol, showing that we could reduce cataracts and improve the

IA Research Notes

Intracameral antibiotics entered the spotlight when a study by the European Society of Cataract and Refractive Surgeons (ESCRS) found that the rate of endophthalmitis was 5 times higher in those who did not receive an IA injection.[1] "The results also showed that there was no statistical benefit in adding perioperative topical antibiotics along with intracameral antibiotics," said Dr. Shorstein.

The study has received its fair share of criticism over the years, however, particularly with regard to its design,[2,3] and additional randomized clinical trials are needed.

Kaiser study. Dr. Shorstein and his colleagues[4] found the following in a study of 300,000 surgeries:

- IA reduced the incidence of endophthalmitis by about half, with no measurable differences between cefuroxime and moxifloxacin.
- Adding topical antibiotics to a regimen of IA did not further reduce the risk of endophthalmitis. In fact, doing so actually increased the risk of endophthalmitis, a finding that was not statistically significant. Dr. Shorstein suspects that any increase could be due to bottle tip contamination, patient error in administration, or trauma to the eye from applying drops.
- Patients on topical fluoroquinolone or polymyxin/trimethoprim alone experienced a significantly lower incidence of endophthalmitis compared to those who failed to fill their prescription for drops and to those on a topical aminoglycoside.

Up next. An ASCRS study is set to compare topical and intracameral moxifloxacin. The hope is that the investigation will lead to FDA approval of an intracameral indication for this existing antibiotic drug, Dr. Greenwood said.

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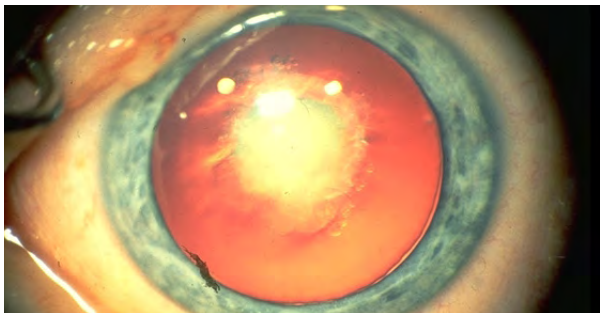

DISSOLVING CATARACTS? *Research on drops to dissolve cataracts began with a fortuitous discovery linking congential cataracts (shown here) with mutations in the* LSS *gene.*

clarity of the lens."

His team then did an experiment in live dogs. "After 6 weeks of treatment using lanosterol eye drops, we were also able to reduce cataracts and significantly increase lens clarity." Although 6 weeks was sufficient to reduce cataracts, he said, cataracts may recur, so retreatment may be needed. An eyedrop treatment has now been developed for treating cataracts in animals.

New nanoparticle. Now, Dr. Zhang and his team are turning their attention to developing a lanosterol eyedrop for humans. The biggest stumbling block has been the molecule itself, which is large and not easily soluble.

"But we have found a nice nanoparticle vehicle and developed a formula that can be used for delivery," he said, explaining that the nanoparticle facilitates lanosterol crossing the cornea by creating an amphipathic molecule, which has both hydrophilic and hydrophobic parts. The lanosterol formula can be delivered as either an eye drop or by implantation, he said, and he added that his team "implanted this nanoparticle gel into the subconjunctival space in monkeys and found it can perform sustained delivery for 2-3 months."

VP1-001. Another research team, at ViewPoint Therapeutics in San Francisco, is working on a second eyedrop. In a study published in *Science*, they reported on a compound that stabilized lens crystallin proteins and prevented them from forming amyloids. The compound, now named VP1-001, improved lens transparency in murine models of hereditary cataract.[7] It also showed promise in aged mouse and human lenses.

Next up: Studies in humans. "In the last quarter of this year, we are going to initiate both human trials and animal studies in the United States and China," said Dr. Zhang. He plans to enroll between 30 and 50 people in the phase 1 safety study, but expects toxicity to be minimal given the endogenous nature of lanosterol.

Looking ahead. Although cataract-dissolving eyedrops are unlikely to be used for rock-hard cataracts, Dr. Zhang sees this approach as a promising alternative to surgery in other instances—for example, with patients who are at risk of complications because they have certain eye conditions (such as weak zonules), bleeding disorders, and/or cardiovascular conditions.

The drops also might be appropriate for those patients who are bothered by symptoms such as glare or trouble seeing in dim light, but their symptoms are not considered severe enough to justify cataract surgery. Finally, eye drops could be widely distributed in remote, resource-scarce areas where surgery is difficult to deliver or even unavailable—and where the burden of cataract-related blindness is greatest.

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MEET THE EXPERTS

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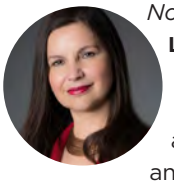

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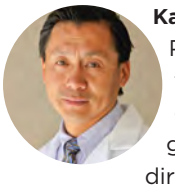

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See disclosure key, page 8. **For full disclosures,** see this article at aao.org/eyenet.

INDICATION[1]

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

IMPORTANT SAFETY INFORMATION[1]

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, blastomycosis, 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 use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- 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.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc.

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

HUMIRA®
adalimumab
destination you™

F1RST AND ONLY FDA-APPROVED ANTI-TNF FOR TREATING NON-INFECTIOUS (NI) UVEITIS*

For adult patients with non-infectious (NI) intermediate, posterior, and panuveitis[1]

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

HUMIRA is proven to[1]:

- Provide steroid-sparing efficacy
- Prolong time to a combined measure of disease flare† and decrease of visual acuity

Visit www.HumiraPro.com/uveitis to learn more.

*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.

abbvie

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. 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, blastomycosis, 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 with chronic or recurrent 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 *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing 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 these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

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 confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) plaque psoriasis (Ps), hidradenitis suppurativa (HS), and uveitis (UV) malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

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 *[see Boxed Warning]*. 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 the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

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 of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating 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.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

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 *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

Clinical Trials Experience

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. 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 antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
Adverse Reaction (Preferred Term)	(N=705)	(N=690)
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions and Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other

week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. 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 HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

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

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [*see Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

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 IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection 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.

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 severe allergic reactions. 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 persistent fever.

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Ref: 03-B374 Revised July 2016

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Put On Your Audit Armor, Part 2: Create Payer-Specific Checklists

The best way to audit-proof your practice is to adhere to payer-specific checklists. This month's Savvy Coder gets you started on a checklist for cataract surgery.

Note: According to a 2014 Office of Inspector General report, when the only diagnosis is cataract(s), Medicare does not cover testing other than one comprehensive eye examination (or a combination of brief/intermediate examinations not to exceed the charge of a comprehensive examination) plus an appropriate ultrasound scan.

Know Your MAC's Policies

Under Medicare Part B, the United States is divided into several jurisdictions, with a Medicare Administrative Contractor (MAC) assigned to each one. These MACs can develop their own coverage policies, known as Local Coverage Determinations (LCDs).

Important! Go to aao.org/lcds, read the LCDs that affect your state, and incorporate their requirements into your payer-specific checklists.

Medicare Cataract Surgery

Make sure that your payer-specific checklist addresses the issues below, and advise physicians not to close out a chart until *all* of the checklist's requirements have been met.

Ensure that you have documented:

- the patient's chief complaint;
- the impact that decreased vision has on activities of daily living (ADL) unique (never cloned) to each patient;
- best-corrected visual acuity (note that most MACs don't have a visual acuity requirement—the exceptions are CIGNA for Kentucky and Ohio, which requires "20/50 or worse," and First Coast for Florida and Puerto Rico, which requires "worse than 20/40");
- physical findings of the cataract;
- that the patient has been educated by the surgeon about the risks and benefits of surgery and the alternative to surgery, and has provided informed consent; and
- that the patient desires surgery.

Verify the diagnosis code. Also, be sure the surgery code is linked to a covered ICD-10 code.

Check the indication(s) for lens removal. These may include the following:

- Monocular diplopia due to a cataract in the affected eye.
- Worsening angle closure due to increase in size of the crystalline lens.
- A significant cataract in a patient who will be undergoing concurrent surgery in the same eye, such as a trabeculectomy or a corneal transplant when the surgeon deems that the decreased morbidity of single-stage surgery is of significant benefit compared with surgery on separate dates.
- Intolerable anisometropia or aniseikonia uncorrectable with glasses or contact lenses that exists as a result of lens extraction in the first eye (despite satisfactorily corrected monocular visual acuity).

Your MAC might cover lens removal in the following situations:

- When an unimpeded view of the fundus is mandatory for proper management of patients with diseases of the posterior segment of the eye(s).
- During vitrectomy procedures if it is determined that the lens interferes with vitreoretinal dissection at the far periphery and excision of the vitreous base, as in cases of proliferative vitreoretinopathy, complicated retinal detachments, and severe proliferative diabetic retinopathy.

Unique to Novitas. If your MAC is Novitas, your documentation must also show the following:

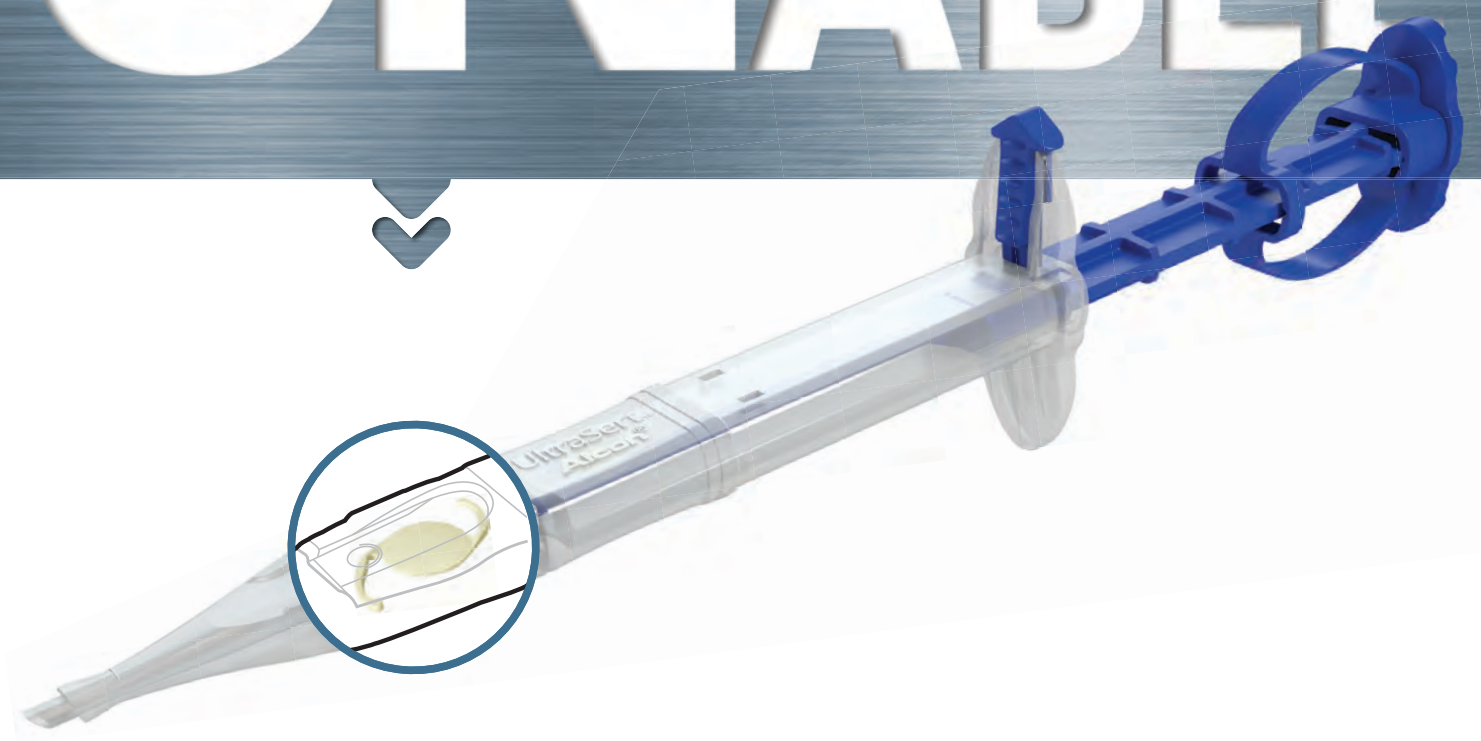
- The patient has undergone the Pre-Cataract Surgery Visual Functioning Index (VF-8R) questionnaire. The questionnaire must be maintained in the patient's medical records and be available upon request. (VF-8R is available at aao.org/practice-management/coding/updates-resources.)
- The length of time between the exam to determine the need for surgery and the surgical date isn't more than 90 days.

Is Novitas your MAC? Novitas is the MAC for the District of Columbia and for the following states: Arkansas, Colorado, Delaware, Louisiana, Maryland, Mississippi, New Jersey, New Mexico, Oklahoma, Pennsylvania, and Texas.

BY **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT.

EXTRA **MORE ONLINE.** For more resources, see this article at aao.org/eyenet.

UNTOUCHABLE



The UltraSert® Pre-loaded Delivery System delivers a pristine optic in less time.[1,2]

Complement your surgical performance with predictable IOL implantations and enhance your cataract outcomes[1-6]:

- **Pristine optic:** Pre-loaded to reduce the risk of IOL damage or contamination versus manual IOL injectors[1]
- **Less time:** Reduces device preparation time and total case time by eliminating manual IOL loading*[,2]

Talk to your Alcon representative to find out how the optimized UltraSert® provides untouchable performance.

*Time and motion study (n=168) comparing UltraSert® pre-loaded Delivery System vs. MONARCH®. Primary endpoint: mean intraoperative lens delivery time (time from device touching eye to trailing haptic leaving the plunger) was not shorter for UltraSert® (p=0.9833). Secondary endpoint: mean intraoperative surgical case time (device prep + lens delivery) was shorter for UltraSert® (p<0.05). Exploratory evaluations: mean device prep time (time from opening package to IOL ready for implantation) and mean total surgical case time (device prep + lens delivery + lens positioning/unfolding) were less with UltraSert® (p<0.05). Mean lens positioning/unfolding (time from lens delivery through time for IOL to unfold) showed no statistical difference (p>0.05).

1. Weston K, Nicholson R, Bunce C, Yang YF. An 8-year retrospective study of cataract surgery and postoperative endophthalmitis: injectable intraocular lenses may reduce the incidence of postoperative endophthalmitis. *Br J Ophthalmol*. 2015;99(10):1377-1380. 2. Goldberg D, Coyle K, Jones M, Lane S, Kim T, Keith M. U.S. multicenter study of time, operational and economic efficiencies associated with using a new preloaded IOL delivery system. Paper presented at: ASCRS-ASOA Symposium and Congress; May 5-9, 2017; Los Angeles, CA. 3-5. Alcon data on file. 6. AcrySof® IQ UltraSert® Pre-loaded Delivery System Directions for Use.

For Important Product Information, please see the next page

Alcon A Novartis Division

UltraSert® PRE-LOADED DELIVERY SYSTEM | AcrySof® IQ ASPHERIC IOL

MIPS Glossary, Part 2: How CMS Talks About Promoting Interoperability, Quality, and More

The Merit-Based Incentive Payment System (MIPS) introduced a slew of new jargon. In August, part 1 of *EyeNet*'s glossary covered some general terminology, as well as the cost and improvement activities performance categories. Part 2 covers the remaining 2 performance categories—promoting interoperability and quality—as well as bonuses and penalties.

Promoting Interoperability Performance Category

This *performance category* was formerly known as *advancing care information.*

2014- and 2015-edition CEHRT. A 2014- or 2015-edition *certified electronic health record technology (CEHRT)* is an EHR system that has been certified as capable of performing measures from the *2018 promoting interoperability transition measure set;* a 2015-edition CEHRT is also capable of performing measures from the *2018 promoting interoperability measure set.*

2015-edition CEHRT bonus. If you report only 2018 promoting interoperability measures and performed them for at least 90 days using only *2015-edition CEHRT,* you can earn a 10% bonus for your *promoting interoperability performance category score.*

2018 promoting interoperability measure set. This set of measures evolved out of the stage 3 measures of the *meaningful use* program.

2018 promoting interoperability transition measure set. These measures evolved from the modified stage 2 measures of the *meaningful use* program.

Advancing care information (ACI) performance category. Until April 2018, the *promoting interoperability performance category* was known as advancing care information (ACI). Because this name change took place so recently, the ACI term appears in many MIPS resources.

Base score. The base score represents a mandatory core level of participation in the *promoting interoperability performance category.* It is an all-or-nothing score: If you successfully perform (or, in some cases, claim an exclusion for) your base score measures, you will max out your base score, and this contributes 50% to your *promoting interoperability performance category score;* fall short, and you will score 0%. Furthermore, you can earn a *performance score* and bonus points only if you first attain a base score (i.e., if your base score is 0%, your promoting interoperability score as a whole is 0%).

Base score measures. There are 4 base score measures in the *2018 promoting interoperability transition measure set,* and 5 in the *2018 promoting interoperability measure set.* For each measure set, 2 of the base score measures are strictly mandatory and the others must be performed unless you qualify for an *exclusion.*

Certified electronic health record technology (CEHRT). CEHRT is an EHR system, or module of an EHR system, that has been certified by the Office of the National Coordinator for Health Information Technology (ONC) as capable of meeting the requirements of the MIPS *promoting interoperability performance category.*

CEHRT for improvement activities bonus. This bonus is based on what you report in the *improvement activities performance category.* Of the 24 improvement activities that can be manually reported via the *IRIS Registry,* 6 of them are eligible for this bonus. If you perform any 1 of those 6 using CEHRT functionalities and attest to doing so in your MIPS reporting, you will earn the full 10% bonus.

Decile-based scoring. For most *performance score measures,* you can earn up to 10% toward your *performance score* depending on which decile your *performance rate* lands in (earn 1% if your performance rate is 1%-10%, earn 2% if it is 11%-20%, etc.).

Exception. If you receive an exception, you don't have to participate in the *promoting interoperability performance category.* This category's contribution to your *MIPS final score* will be *reweighted* to zero, with that weight being reassigned to the *quality performance category.* Some exceptions are automatic; others you must apply for. You automatically qualify for an exception if CMS considers you to be a hospital- or ASC-based clinician, a

BY **SARAH CARTAGENA,** ACADEMY HEALTH POLICY SPECIALIST, **CHRIS MCDONAGH,** *EYENET* SENIOR EDITOR, AND **JESSICA PETERSON, MD, MPH,** ACADEMY MANAGER OF QUALITY AND HIT POLICY.

non-patient–facing clinician, a nurse practitioner, a physician assistant, a clinical nurse specialist, or a certified registered nurse anesthetist. You must apply for the significant hardship, small practice, and CEHRT decertification exceptions. Note: If you report any promoting interoperabilty measures, you will waive your right to any exception that you might have received.

Exclusion. You may qualify for an exclusion for some *base score measures.* This allows you to attain a *base score* without performing that measure. For example, if you write fewer than 100 prescriptions during your promoting interoperability performance period, you can be excluded from the e-prescribing *base score* measure.

Meaningful use. Before MIPS, the Medicare and Medicaid EHR Incentive Program—also known as the meaningful use program—used a carrot-and-stick approach to encourage the adoption of *certified EHR technology.* This program was absorbed into MIPS and is now known as the *promoting interoperability* performance category.

Performance score. If you attain the *base score,* you also can attain a performance score, which can contribute up to 90% to your *promoting interoperability performance category score.*

Performance score measures. Performance score measures can contribute to your *performance score* (0%-90%). Most are optional, but some are also *base score measures* and are therefore mandatory (unless an *exclusion* applies).

Promoting interoperability performance category. This is 1 of 4 performance categories in MIPS; it was previously named *advancing care information* (ACI). It replaced the *meaningful use* program for EHRs.

Promoting interoperability performance category score. This score, which is capped at 100%, is the sum of your *base score* (50%), *performance score* (0%-90%), *registry/agency bonus* score (0% or 5%), *CEHRT for improvement activities bonus* score (0% or 10%), and *2015-edition CEHRT bonus* score (0% or 10%). Your promoting interoperability score contributes up to 25 points to your *MIPS final* score (e.g., a score of 80% contributes 20 points).

Registry/agency bonus score. Earn a 5% bonus by reporting at least 1 bonus measure that involves active engagement, through EHR integration, with a clinical data registry or public health agency. Note: This can't be the same entity that you referenced when attesting for your *performance score.*

Quality Performance Category

This performance category evolved from the Physician Quality Reporting System.

Achievement points. For each *quality measure,* you can receive achievement points based on how your performance compares against a *benchmark* for that measure. If CMS can't make that comparison—either because a measure lacks a *benchmark* or you failed to meet the *case minimum requirement* and satisfy the *data completeness criteria*—you may still earn minimal achievement point(s) for reporting it.

All-cause hospital readmission (ACR) measure. The ACR measure only applies to *large practices* that have a large volume of patients (at least 200) who experience an unplanned readmission to hospital within 30 days of initial discharge. It is unlikely to apply to many ophthalmic practices.

Benchmark. Many MIPS *quality measures* and *QCDR quality measures* have performance benchmarks, divided into deciles; the *achievement points* you receive for a measure will depend on which decile your performance falls into, and where it lands within that decile. For example, if your performance rate is in the 3rd decile, you can score 3.0-3.9 achievement points. There are different benchmarks for different *reporting mechanisms.* The benchmarks for the 2018 *performance year* are typically based on performance data from 2016. If there wasn't enough 2016 data to set a benchmark for a measure, CMS will try to set a benchmark based on 2018 performance data; if CMS is unable to do that, you can only score 3 achievement points for that measure (or 1 point, if you don't meet the *data completeness criteria* and are in a large practice).

Benchmarks are included in the Academy's detailed description of each measure (aao.org/medicare/quality-reporting-measures).

Bonus points. When you report a measure, you can earn a CEHRT *end-to-end bonus point* and/or *high priority bonus point(s).*

Case minimum requirement. You won't be able to score more than 3 *achievement points* for a measure unless you meet the case minimum requirement (report on at least 20 patients) and satisfy the *data completeness criteria.* The *ACR measure* is an exception: Its case minimum requirement is 200 patients.

CEHRT bonus point. See *end-to-end reporting bonus point.*

Claims-based reporting. If you report as an individual, you can report *MIPS quality measures* via Medicare claims. The process should be familiar if you used to report PQRS measures by claims: Enter appropriate quality data codes (QDCs) into your CMS form 1500. Make sure you use the right QDCs, as some have changed. There are drawbacks to claims-based reporting: Many measures are *topped out* at a low decile, it must be done in real time, and it is less efficient than manual reporting via the *IRIS Registry.*

Consumer Assessment of Health Providers and Systems (CAHPS) for MIPS survey. A data submission mechanism that can be used as a second reporting mechanism for *quality;* however, it is not applicable for most ophthalmologists.

Data completeness criteria. For a *quality measure,* report on at least 60% of patients for whom that measure applies (detailed specifications for each measure, including lists of relevant codes, are available at aao.org/medicare/quality-reporting-measures). Include both Medicare and non-Medicare patients (unless reporting via Medicare claims, in which case only include the former). If you don't meet the 60% threshold, but do report on at least 1 patient, you will score 1 achievement point if you are part of a large practice, 3 if part of a small practice.

Eligible measure applicability (EMA). If you report fewer than 6 measures, CMS may use the EMA process to see

if there were other available measures for you to report. This process is only applied to those who report by claims or a *qualified registry.*

End-to-end reporting bonus point. Awarded for reporting a *MIPS quality measure* or *QCDR quality measure* using electronic end-to-end reporting. This can include measures reported via IRIS Registry/EHR integration or your EHR vendor. You can score a maximum of 6 bonus points for end-to-end reporting (or 7 if the *ACR measure* applies to you).

High-priority bonus points. Awarded for reporting more than 1 *high-priority measure.* Note: To earn this bonus for a measure, your reporting must meet the *case minimum requirement* and the *data completeness criteria.* You can score a maximum of 6 high-priority bonus points (or 7 if the *ACR measure* applies to you).

High-priority measure. An outcome, appropriate use, patient safety, efficiency, patient experience, or care coordination quality measure. Note: CMS has been inconsistent in how it describes *outcome measures.* Although it lists them as a type of high-priority measure, it also sometimes refers to them as if they are distinct from high-priority measures (e.g., "include 1 outcome or high-priority measure").

Improvement percent score. Rewards those who score more quality *achievement points* in 2018 than in 2017.

Inverse measure. For most measures, a higher *performance rate* means you will score more *achievement points* (i.e., you would score more with a 90% performance rate than with an 80% rate). However, with an inverse measure—e.g., Measure 1: Diabetes: Hemoglobin A1c (HbA1c) Poor Control (>9%)—a lower performance rate means a higher score. Specifically, you want the percentage of patients with poor control of HbA1c to be as low as possible.

Measure achievement points. The score assigned to you based on how your *performance rate* for a measure compares against that measure's *benchmark.*

MIPS quality measures. Standard quality measures that are published in the MIPS regulations. (Compare with the *QCDR quality measures.*)

Outcome measure. A *high-priority measure* that measures a clinical outcome.

QCDR quality measures. Specialty-specific measures developed by qualified clinical data registries, such as the *IRIS Registry.*

Quality measures. CMS sometimes uses the term *quality measures* to refer to those measures that were published in the MIPS regulations, as opposed to the QCDR quality measures. However, you also see this term used when referring to both types of measure.

Quality performance category. This performance category involves reporting quality measures and typically contributes up to 50 points to your *MIPS final score.* It evolved out of the Physician Quality Reporting System (PQRS).

Quality performance category achievement percent score. This score, which is used when calculating your *improvement percent score,* factors in *achievement points* but not *bonus points.*

Quality performance category percent score. This score (0%-100%) determines how many points (0-50 points) the *quality performance category* contributes to your *MIPS final score;* for example, a 50% score would contribute 25 points to your MIPS final score.

Topped out. Some measures have a *benchmark* that reaches, or almost reaches, perfect performance well before the 10th decile. CMS frowns on such measures, because a large percentage of clinicians reporting those measures will have minimal room for improvement. It designates such measures as *topped out.* For most topped out measures, you need a perfect performance to score 10 points; fall short and there is a ceiling on how many *measure achievement points* you can earn for it. Let's say you report measure 12: Primary Open Angle Glaucoma: Optic Nerve Evaluation. If your performance is less than perfect, there is a ceiling of 3.9 *measure achievement points* when reporting by claims and 5.9 points when reporting manually via the *IRIS Registry.*

Total available measure achievement points. This is typically either 60 points or, in the unlikely event that the *ACR measure* applies, 70 points. It is used as the *denominator* when calculating your *quality performance category achievement percent score.*

Total measure achievement points. The sum of your *measure achievement points* for up to 6 reported measures plus, if applicable, the *ACR measure.*

Payment Adjustments

Your *MIPS final score* (0-100 points) for 2018 will impact your payments for Medicare Part B services in 2020:

- Score less than the 15-point *performance threshold*, and you will get a penalty (negative *payment adjustment factor*).
- Score above that threshold, and you will get a small bonus (positive *payment adjustment factor*).
- Score above the 70-point *additional performance threshold* and you also will get a second bonus for exceptional performance (an *additional payment adjustment factor*).

Additional payment adjustment factor. This is the bonus for exceptional performance (meeting or exceeding the *additional performance threshold*). It is on a sliding scale (the higher your score, the bigger the adjustment), is funded by a $500 million bonus pool, and is in addition to your positive *payment adjustment factor.*

Additional performance threshold. This 70-point threshold sets the bar for exceptional performance.

Exceptional performance bonus. An alternate term for the *additional payment adjustment factor.*

Payment adjustment. Your payment adjustment includes a *payment adjustment factor* and, if applicable, an *additional payment adjustment factor.*

Payment adjustment factor. Depending on whether your *MIPS final score,* falls below, meets, or exceeds the 15-point *performance threshold,* your payment adjustment factor will be negative (penalty), neutral (no penalty, no bonus), or positive (small bonus, on a sliding scale). These adjustments will be budget neutral, with the penalties funding the bonuses.

Performance threshold. Your 2020 *payment adjustment factor* will be positive, neutral, or negative, depending on whether your 2018 *MIPS final score* exceeds, meets, or falls below a 15-point performance threshold.

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2018 Orbital Gala

Join Your Cool Academy Cats for an Outta-Sight Night

Get hip to the AAO 2018 scene and let your psychedelic prints fly at the Academy Foundation's 1960s-themed Orbital Gala-a-go-go. At this 15th annual fundraiser, you'll support our quest to protect sight and empower lives while showing off your favorite love beads and scarfing down far-out food and cocktails. Take your groovy moves to the dance floor and catch some live jams; or if that's not your bag, throw some bread at the silent auction. Proceeds support Academy programs. Dig it?

Chicago Cultural Center

Sunday, Oct. 28
6 to 10 p.m.

To purchase tickets, visit aao.org/foundation

Foundation

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

This Year's Laureate: Steven T. Charles, MD

The Board of Trustees of the Academy is proud to announce **Steven T. Charles, MD,** as the recipient of the 2018 Laureate Recognition Award. Dr. Charles is currently a clinical professor at the University of Tennessee and runs the Charles Retina Institute, an internationally recognized clinic performing both retinal treatment and research.

The road to success. From a young age, Dr. Charles defined himself by commitment to his 3 T's: technique, technology, and teaching. After attending university for engineering, Dr. Charles enrolled in medical school in 1965 at the University of Miami, where he conducted research at the fledgling Bascom Palmer Eye Institute under the guidance of Edward W.D. Norton, MD. He then accepted a medical internship and residency in ophthalmology at Jackson Memorial Hospital in Miami, and in 1973, he served as a clinical associate at the National Eye Institute. A retina specialist, Dr. Charles has since dedicated himself to improving patients' lives and to innovating ophthalmologists' practices in the field of retina.

Efforts rewarded. Through a combination of his own expertise and collaboration with others, Dr. Charles has played a major role in developing countless surgical techniques, including endophotocoagulation, fluid-air exchange, forceps membrane peeling, and linear suction, to name a few. Accordingly, he has more than 100 issued or pending patents. Dr. Charles is both the founder of MicroDexterity Systems, which developed robots to aid in spine surgery and minimally invasive knee and hip replacements, and the cofounder of CamPlex, a company pioneering advanced visualization technology for neurosurgery and the treatment of head and neck cancers.

ACADEMY LAUREATE: STEVEN T. CHARLES, MD. *The Laureate Recognition Award honors physicians who have made the most significant contributions to ophthalmology leading to the prevention of blindness and restoration of sight worldwide.*

Dr. Charles is most proud of his work at Alcon Laboratories, where he served as principal architect for the Accurus Surgical System and Constellation Vision System. These systems, through Dr. Charles' innovative technological design and through his willingness to train other ophthalmologists, have revolutionized vitreous surgery worldwide.

A life of achievement. In addition to creating many new surgical techniques and technologies, Dr. Charles has performed over 37,000 vitreoretinal surgeries, lectured in 50 countries, delivered 17 named lectures, and embarked on more than 1,000 speaking trips. He has authored more than 170 articles and 50 book chapters. His *Vitreous Microsurgery,* a leading textbook in the field, is in its fifth edition and has been published in 6 languages.

Honored in Chicago. In recognition of Dr. Charles' contributions to ophthalmology, the Academy will honor him as the 2018 Laureate during the Opening Session of AAO 2018 in Chicago.

At AAO 2018, read an interview with Dr. Charles about his life and accomplishments in *AAO 2018 News,* a convention tabloid distributed onsite.

Annual Business Meeting

Notice is hereby given that the Annual Business Meeting of the American Academy of Ophthalmology will be held Sunday, Oct. 28, from 8:30-10:30 a.m. in Room E354 at the McCormick Place Convention Center in Chicago. Candidates for membership will be approved during this meeting.

For the full list of names, visit aao.org/member-services/candidates. To see the full order of business, refer to the "Opening Session" page of the *Meeting Program.*

AMERICAN ACADEMY OF OPHTHALMOLOGY®

TAKE NOTICE

The Foundation's 2017-2018 Annual Report

In the field of eye health, the Academy leads the way. Last year was yet another success, in large part because of our members' generosity and dedication to our mission. Read the Foundation's latest annual report to learn about the impact of our key initiatives during the 2017-2018 fiscal year, including the following:

- The IRIS Registry reached 200 million patient visits, collecting data that can profoundly improve patient care.
- The Education Distribution Project provided textbook donations to ophthalmologists in places such as Cameroon, the Ukraine, and South Africa.
- EyeCare America referred more than 8,000 medically underserved seniors and others at increased risk for eye disease to our dedicated volunteer ophthalmologists.
- The Ophthalmic News and Education (ONE) Network launched the David E.I. Pyott Glaucoma Education Center in fall of 2017. This center was made possible by a $2 million gift from David E.I. Pyott, CBE, MD(Hon).
- Stanley M. Truhlsen, MD, pledged $4 million in matching funds to build a new home for the Museum of Vision.

View the report at aao.org/foundation.

Stay Current With @AAOjournal

Use Twitter to keep up with the latest research from *Ophthalmology, Ophthalmology Retina,* and the Academy's newest peer-reviewed journal, *Ophthalmology Glaucoma.* Every day the journals post new content, including articles in press, clinical images, thought-provoking editorials, and new issue alerts.

Follow the journals today @AAOjournal or https://twitter.com/AAOjournal.

Urgent MIPS Notice—Get Started on Your 90-Day Performance Periods

Under the Merit-Based Incentive Payment System (MIPS), you will be evaluated on up to 4 performance categories. Two of these—promoting interoperability and improvement activities—each have a performance period that must be at least 90 consec-

EYECARE AMERICA PATIENT STORY

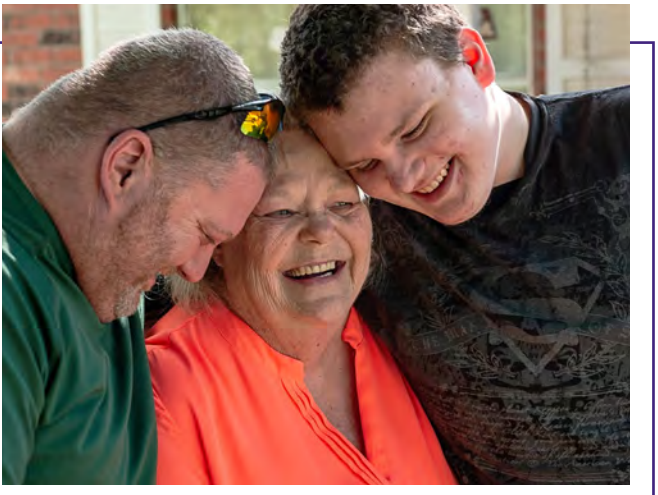
My Vision Was Limiting My Life

The Academy's EyeCare America (ECA) program has helped nearly 2 million people since its inception in 1985, and it is one of the largest public service programs in American medicine. Approximately 2,000 of ECA's current volunteers have been with the program since it began and will, naturally, be retiring, thus reducing access to care for underserved populations. To mitigate this, the Academy urges the next generation of members to participate in ECA. The commitment is minimal—ECA volunteers see only 2 to 4 patients on average per year.

Patient story. "By the time I was 13 years old, I had spent so much unprotected time in the sun that my doctor made me wear wrap-around dark sunglasses to protect my eyes from further damage. For the next 50 years, I've had to depend on wearing eyeglasses to get around. Recently my vision became so much worse that even eyeglasses were no longer helping. I could no longer see the keys to play the piano or putter in my garden, one of my favorite pastimes.

"My niece found ECA online and emailed me the link to pass on to my sister, her 78-year-old mother. My vision had become so limited that I decided to see if I was eligible for eye care as well. Every extra penny I have goes to paying bills and just getting by. I had nothing extra to pay for an eye exam, let alone any follow-up care I might need. EyeCare America made this process so easy; the office even sent me a reminder with directions to my appointment.

"Dr. Conley was amazing. He restored my sight by removing my cataracts. The surgery was pain-free and so successful that I still can't get used to not reaching for my eyeglasses. Thank you, EyeCare America, for caring about people like me. I worked hard all my life on rotating shifts in factories. My vision was limiting everything I did. I'm now back to playing the piano, gardening, and seeing my son and grandson more clearly."



FAMILY TIME. *With renewed vision, patient Betty White can more easily spend time doing various activities with her son and grandson.*

Ryan P. Conley, DO, on ECA. "Serving others is always a blessing, and I'm thankful for the opportunity to provide patients with the eye care they so desperately need. The Eye Care America program has filled an important health care gap for these patients, and we're proud to help further the program's mission here in our community."

Sign up to volunteer at aao.org/volunteer.

utive days and that must be completed no later than Dec. 31, 2018. (For the other 2 performance categories—quality and cost—the performance period is the full calendar year.)

Score 100% for improvement activities. All ophthalmologists should be able to max out their score for the improvement activities performance category, which would be enough to avoid the MIPS payment penalty.

To perform promoting interoperability measures, you need an electronic health record (EHR) system. The promoting interoperability performance category evolved out of the EHR meaningful use program. (In the first year of MIPS, this performance category was known as advancing care information. CMS changed the name in April.)

How to start. Visit aao.org/medicare for detailed descriptions of the promoting interoperability measures and the 24 improvement activities that are most relevant to ophthalmology. You also can visit aao.org/eyenet/mips-manual-2018 to download *EyeNet*'s 60-page MIPS manual, which includes at-a-glance lists that link to those detailed descriptions.

Don't delay. Do not wait until the last moment (Oct. 3) to start performing improvement activities and promoting interoperability measures. An earlier start will provide you with some leeway if you run into difficulty with your MIPS procedures. Once you have completed your performance period, you can use the IRIS Registry web portal to manually attest to your performance. Note: The performance period for promoting interoperability does not have to start on the same day as the performance period for improvement activities.

What about the 12-month performance periods? The performance periods for quality and cost started on Jan. 1. If you met the deadlines for integrating your EHR system with the IRIS Registry, quality measure data will be extracted from your EHR; once the performance year is over, the IRIS Registry will select and report the measures that should provide you with your highest quality score. The next best option would be to manually report quality measures via the IRIS Registry web portal. For the cost measures, you don't have to report anything; CMS will evaluate you based on claims data.

D.C. REPORT

Big Changes Proposed for E&M Documentation in 2019

The Academy is anxiously awaiting the final fee schedule rule for 2019, which the Centers for Medicare & Medicaid Services (CMS) is likely to release in October or early November. One of CMS' biggest proposed changes for next year is a simplified, single-tiered approach to both documentation and payment when using the level 2 through 5 E&M codes.

What does this mean for reimbursement? The Academy's health policy experts believe that practices that bill for E&M levels 4 and 5 would receive lower payment under the proposed plan, but they could instead opt to bill using existing Eye visit codes. This change would primarily affect some of ophthalmology's subspecialists.

Payment under CMS' 2019 proposed plan would be between a level 3 and 4 code: $135 for a new patient and $93 for an established patient. By comparison, a current level 4 new-patient E&M code pays on average $167; an established patient, $109.

More options for documenting an E&M visit. One intent of the proposed change is to reduce the documentation burden. While the exact details aren't yet known, it is proposed that you could 1) continue to use the current framework for documenting E&M visits (i.e., include history, exam, and medical decision-making) or use either 2) medical decision-making or 3) time to demonstrate the scope of the visit.

A minimum standard of documentation for E&M codes. Under the proposed regulations, those who bill E&M codes levels 2 through 5 should note the following:

- If you continue to use the current framework, documentation would need to meet or exceed the 2018 level 2 requirements for the history, exam, and medical decision-making.
- If you decide to use medical decision-making alone, you would need to meet or exceed the documentation that is currently required for that component of a level 2 E&M visit.
- If you plan to document time, stay tuned: CMS is still determining how much face-to-face time would be needed to support use of these codes.

MIPS: Sign Up for the IRIS Registry Portal by Oct. 31

The IRIS Registry is ophthalmology's tool of choice for reporting the Merit-Based Incentive Payment System (MIPS). You can use the IRIS Registry web portal to manually report quality measures, promoting interoperability measures, and improvement activities.

Who needs to sign up? If you reported MIPS via the IRIS Registry web portal in 2017, you do not have to sign up anew in 2018. If you have already signed up for IRIS Registry/EHR integration, you do not need to sign up separately for the web portal.

Visit aao.org/iris-registry and click "Sign up."

ACADEMY RESOURCES

BCSC Self-Assessment

There is a new tool for residents and practicing ophthalmologists: the *Basic and Clinical Science Course* (*BCSC*) Self-Assessment Program. It includes 1,000+ questions to help identify knowledge gaps, and each answer provides a thorough discussion, excerpts from the *BCSC*, and complete references. This activity has been approved for AMA PRA Category 1 Credit.

Learn more at store.aao.org/bcsc resident.

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When you make a gift to the American Academy of Ophthalmology Foundation, you're supporting innovative programs that educate physicians and improve quality of care at home and around the globe.

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aao.org/foundation

Dr. Blodi performed surgery to repair a retinal detachment in Charles Soderquist's right eye. Says Soderquist, "I would be blind if it wasn't for you."

"The Foundation's mission reminds me why I wanted to be a doctor—to help and give to others. One of the best ways to accomplish this is through donations, particularly at the Partners for Sight level. I am proud to be an ophthalmologist and am excited to contribute to the advancement of the field."

CHRISTOPHER F. BLODI, MD
WEST DES MOINES, IA.

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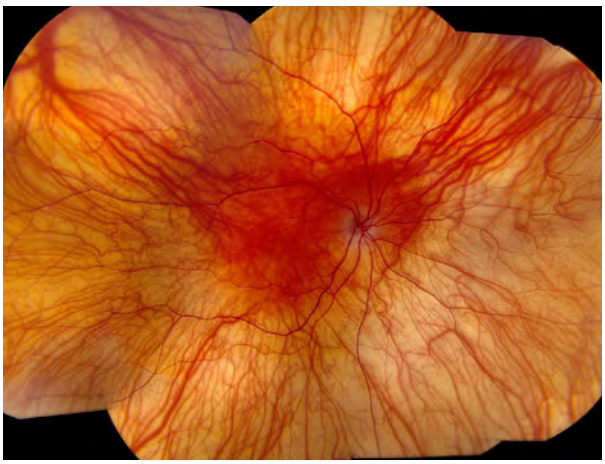

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CYPASS® ULTRA SYSTEM
Important Product Information

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

Indication: The *CYPASS*® Ultra System 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 (POAG).

Contraindications: Use of the *CYPASS*® Ultra System is contraindicated in the following circumstances or conditions: (1) in eyes with angle closure glaucoma; and (2) in eyes with traumatic, malignant, uveitic or neovascular glaucoma or discernible congenital anomalies of the anterior chamber angle.

MRI Information: The *CYPASS*® Micro-Stent is magnetic resonance (MR) Safe: the implant is constructed of polyimide material, a non-conducting, non-metallic, non-magnetic polymer that poses no known hazards in all magnetic resonance imaging environments.

Warnings: Gonioscopy should be performed prior to surgery to exclude peripheral anterior synechiae (PAS), rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard.

Precautions: The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The safety and effectiveness of the *CYPASS*® Ultra System has not been established as an alternative to the primary treatment of glaucoma with medications, in patients 21 years or younger, in eyes with significant prior trauma, chronic inflammation, eyes with an abnormal anterior segment, eyes with chronic inflammation, eyes with glaucoma associated with vascular disorders, pseudophakic eyes with glaucoma, eyes with uveitic glaucoma, eyes with pseudoexfoliative or pigmentary glaucoma, eyes with other secondary open angle glaucomas, eyes that have undergone prior incisional glaucoma surgery or cilioablative procedures, eyes with laser trabeculoplasty performed ≤ 3 months prior to the surgical screening visit, eyes with unmedicated IOP less than 21 mmHg or greater than 33 mmHg, eyes with medicated IOP greater than 25 mmHg, in the setting of complicated cataract surgery with iatrogenic injury to the anterior or posterior segment, and when implantation is without concomitant cataract surgery with IOL implantation for visually significant cataract. The safety and effectiveness of use of more than a single *CYPASS*® Micro-Stent has not been established.

Adverse Events: In a randomized, multicenter clinical trial comparing cataract surgery with the *CYPASS*® Micro-Stent to cataract surgery alone, the most common post-operative adverse events included: BCVA loss of 10 or more letters at 3 months after surgery (8.8% for *CYPASS*® vs. 15.3% for cataract surgery only); anterior chamber cell and flare requiring steroid treatment 30 or more days after surgery (8.6% vs. 3.8%); worsening of visual field mean deviation by 2.5 or more decibels (6.7% vs. 9.9%); IOP increase of 10 or more mmHg 30 or more days after surgery (4.3% vs. 2.3%); and corneal edema 30 or more days after surgery, or severe in nature (3.5% vs. 1.5%).

Attention: Please refer to the Product Instructions for a complete list of contraindications, warnings, precautions and adverse events.

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Saturday, October 27, 2018

United Club Level 1 at Soldier Field • 5:45 PM Registration • 6:30 PM Program

MODERATOR

Ike K. Ahmed, MD, FRCSC

Assistant Professor, University of Toronto, Director, Glaucoma and Advanced Anterior Segment Fellowship, University of Toronto, Research Director, Kensington Eye Institute, University of Toronto

An interactive and unique experience! This symposium will feature a discussion on patient selection, a case review of proven results with *CYPASS*® Ultra System and post-operative management pearls.

Transportation to the event will be provided. **SEATING IS LIMITED!**

REGISTER ONLINE NOW!
https://BIT.LY/SaveSaturdayforCYPASS

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Please see the back of this ad for important product information.

This event is not affiliated with the official program of AAO 2018. Faculty are paid consultants for Alcon.

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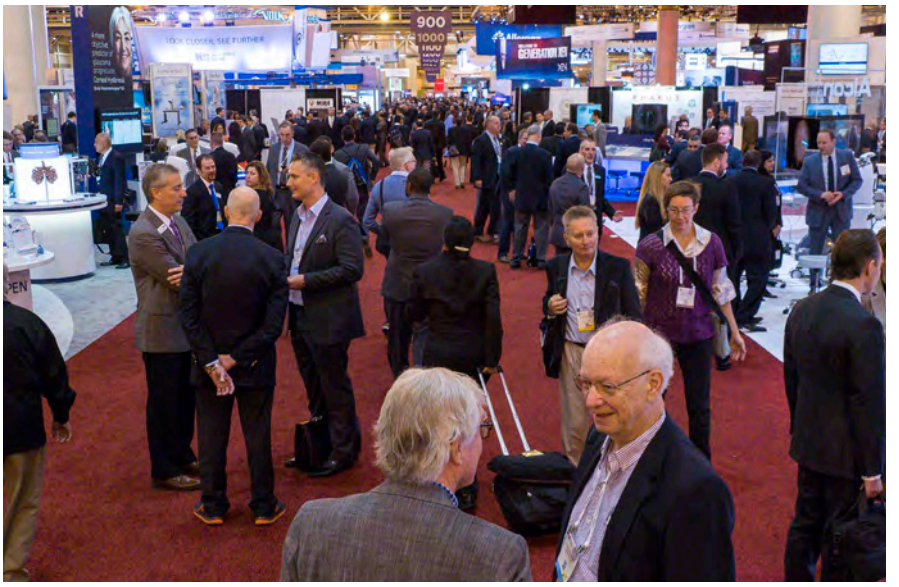
GET READY FOR CHICAGO • PART 5 OF 6



EXHIBITION PREVIEW. *Explore the full list of exhibitors before the meeting at aao.org/exhibition. The Exhibition will be open from Saturday, Oct. 27 through Tuesday, Oct. 30. There also will be an earlier set of retina exhibits on Friday, Oct. 26.*

BEAT THE CLOCK

Avoid Standing in Registration Lines

Maximize your time in Chicago by skipping the onsite registration lines. To have badges and other materials mailed before the meeting, U.S. residents must register online by Sept. 28; international attendees, before Sept. 4. Remember to also purchase the Academy Plus course pass and any tickets that you need. After these dates, you can still register online but will need to pick up registration materials in Chicago.

For more information and to register, visit aao.org/registration.

Avoid Hotel Booking Scams

Beware of fraud! Housing "poachers" are creating illegitimate AAO housing website portals that are unaffiliated with the Academy. Be sure to reserve hotel rooms only through the Academy's official housing provider, Expovision. There are 54 official AAO 2018 hotels to choose from.

Book online. Visit aao.org/hotels for reservations and an interactive map with information on hotel amenities and availability. Reserving a room online is the quickest way to secure a hotel, and you receive immediate confirmation.

Book by phone or email. Agents at Expovision can assist you from Monday through Friday, 8:30 a.m.-5:30 p.m. Eastern Daylight Time. Call 866-774-0487 (toll-free from the United States and Canada) or 703-770-3908 (from elsewhere), or email aaohotels@expovision.com.

HALL HIGHLIGHTS

Preview the Exhibition

Use the Virtual Exhibition to search for exhibitors by company name, booth number, product categories, medical subspecialty, common equipment terms, and basic ophthalmic conditions. Review an exhibiting company's profile, including business contacts and product categories, and view a map showing the companies' locations in the exhibit hall. Log in to the Virtual Exhibition and create a My Expo account to tag exhibitors of interest and create a must-see list for your visit.

For more information, visit aao.org/exhibition.

Attend Product Theater Talks

Visit the Technology Pavilion (Booth 168) to get the latest product news from exhibitors and enjoy a free continental breakfast or afternoon snack. Hear from Nidek, 9:30-10:30 a.m., and Abbvie, 12:30-1:30 p.m., on Oct. 27. Spark Therapeutics will present on Oct. 28, and Sun Ophthalmics, on Oct. 29, both from 9:30-10:30 a.m. These non-CME Product Theater talks are not affiliated with the official program of AAO 2018 or Subspecialty Day. By attending, you may be subject to reporting under the Physician Payment Sunshine Act.

For topics and speakers, visit aao.org/exhibition.

The EyePlay Experience

Take a break at the EyePlay Experience booth and give back to the community, recharge your mobile device in the new Charging Lounge, relieve some stress with therapy animals, challenge a col-

MedMeeting Images, Todd Buchanan (2016, 2017 galleries)

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league to Ping-Pong, take a selfie with a giant #aao2018 hashtag, enjoy a complimentary seated massage, get help at the Tech Bar, or just chill.

Visit Booth 2581, Saturday through Monday from 9 a.m.-5 p.m., and Tuesday from 9 a.m.-1 p.m.

EYEPLAY EXPERIENCE. *Visit Booth 2581 for relaxing activities, including petting therapy dogs.*

EVENTS

Alumni and Related Group Events

Connect with old friends and meet new colleagues at alumni and related events during AAO 2018.

To view the list of get-togethers, visit aao.org/annual-meeting/alumni-events or look in the Mobile Meeting Guide at aao.org/mobile.

Step Up: AAO 2018 Walking Challenge

Sign up online for the Academy's first step challenge. Download the challenge app, which will use the data from your step tracking device to see who goes the farthest. Use the app's QR scanner at designated checkpoints around the convention center to earn extra steps. The grand prize is a free hotel room for AAO 2019 in San Francisco!

For more information, visit aao.org/step.

Save the Dates: *EyeNet* Corporate Lunches

Be sure to leave room in your schedule for *EyeNet*'s free corporate educational lunches from 12:30-1:30 p.m. on Oct. 27-29. This year, learn about diabetic eye disease, dry eye, and cataract surgery from Regeneron Pharmaceuticals, Shire, and Omeros Corporation, respectively.

Complimentary boxed meals are available on a first-come, first-served basis, with lunch pickup beginning at 12:15 p.m.

Located onsite at McCormick Place, these non-CME symposia are developed independently by industry—they are not affiliated with the official program of AAO 2018 or Subspecialty Day. Take note that by attending, you may be subject to reporting under the Physician Payment Sunshine Act.

For topics and speakers, visit aao.org/eyenet/corporate-events.

PROGRAM

Your Mobile Meeting Guide

The Mobile Meeting Guide (MMG), sponsored by Zeiss, is a website optimized for your mobile device. It will be available in mid-September to provide access to myriad useful meeting tools and information, including:

- program content, such as abstracts, handouts, and evaluations;
- a planner to keep track of courses, sessions, and exhibitors to visit;
- maps to course rooms and exhibit hall booths;
- announcements from the Academy;
- a messaging feature to talk to other attendees and presenters; and
- Scientific Posters and Videos on Demand, available for viewing starting Saturday, Oct. 27.

New for 2018, enable messaging in your MMG settings to have reminders, messages, and announcements texted to you during the meeting.

Visit aao.org/mobile.

SUBSPECIALTY DAY

Subspecialty Day Previews: What's Hot

This month, program directors from the Ocular Oncology and Pathology and Retina meetings preview some of this year's highlights. View the program schedules at aao.org/annual-meeting/subspecialty-day.

OCULAR ONCOLOGY AND PATHOLOGY 2018—Hot Topics in Ocular Pathology and Oncology—An Update. ***Program Directors:*** *Patricia Chévez-Barrios, MD, and Dan S. Gombos, MD.* ***When:*** *Saturday, Oct. 27 (8:00 a.m.-5:00 p.m.)*

"This year's Subspecialty Day in ocular oncology and pathology will highlight rapid advances in the field. Personalized care is now standard in oncology, and ophthalmic tumors have benefitted significantly from prognostic testing and mutational analysis. Vigorous debates and roundtables will highlight areas of consensus and disagreement among ophthalmologists. As the use of intra-arterial chemotherapy for retinoblastoma reaches its first decade in some U.S. centers, experts will discuss the treatment's medium- and long-term risks. They will also debate the benefits of tumor prognostication for uveal melanoma in light of its impact on patient survival.

"In addition, numerous clinical trials have now reached completion. We will have a comprehensive review of 4 national multicenter trials within the field of retinoblastoma, sponsored

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ART + SCIENCE
SUBSPECIALTY DAY

by the Children's Oncology Group and presented by the principal investigators of each trial. The program also features presentations about novel therapies for primary uveal melanoma as well as clinical trials for metastatic disease. A well-received session from past meetings—clinical pearls from senior leadership—is back with highlights from Ralph Eagle, MD, Joan M. O'Brien, MD, and Jerry A. Shields, MD.

"New this year will be a session on gender disparity research and a session on late-breaking hot topics, including discussion of the clusters of uveal melanoma patients.

"Both comprehensive ophthalmologists and specialists will be riveted by updates on the latest and most significant advances in the field."

The Ocular Oncology and Pathology meeting is organized in conjunction with the American Association of Ophthalmic Oncologists and Pathologists.

RETINA 2018—The Art + Science of Retina + Vitreous

Program directors: *Richard F. Spaide, MD, and Mark S. Humayun, MD, PhD.*
When: *Friday, Oct. 26 (8:00 a.m.-5:36 p.m.) and Saturday, Oct. 27 (8:00 a.m.-5:28 p.m.).*

"In the process of designing the Retina Subspecialty Day program, we tried to optimize every minute of the 2-day meeting. There are many great features, and all the talks will be highly informative.

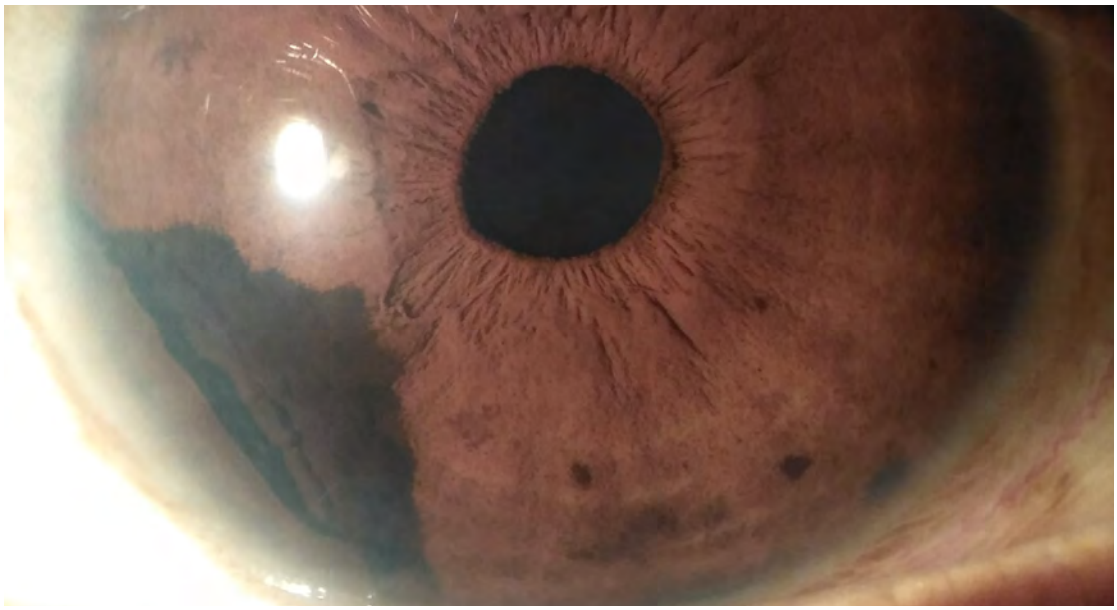
"The program will have something for everyone. Topics range from extensive coverage of vitreoretinal surgery and medical retina to uveitis, pediatric retina, oncology, imaging, diabetic retinopathy, and neovascular and non-neovascular AMD. In past years, surgical videos have proved very popular, so we are bringing them back again this year with 'Video Surgical Complications—What Would You Do?' and 'My Coolest Surgical Videos.' And last year, we launched a session titled 'Innovative Retinal Interventions,' which was very well received. This year, we will reprise it with presentations on topics ranging from nano-retina and gene therapy to the ever-popular imaging session. Of course, we will also include 'Late-Breaking Developments, Part I and Part II.'

"New this year is the Special Lecture. Lily Peng, MD, PhD, will speak about 'Machine Interpretation of Fundus Photography.' Considering that artificial intelligence has been getting much attention recently, we think this lecture should have broad appeal and provide insight into the future of our field. Dr. Peng is in the Google AI Research Group and has coauthored studies on machine learning and diabetic retinopathy in both *Ophthalmology* and *JAMA*. Also new is 'My Best Medical Retina Cases,' a session with 5 case presentations followed by expert discussion."

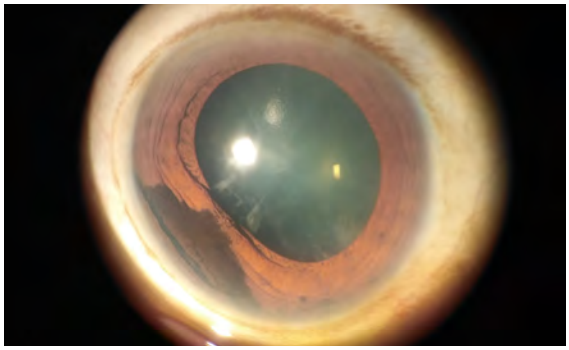
The Retina meeting is organized in conjunction with the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin.

MYSTERY IMAGE

BLINK



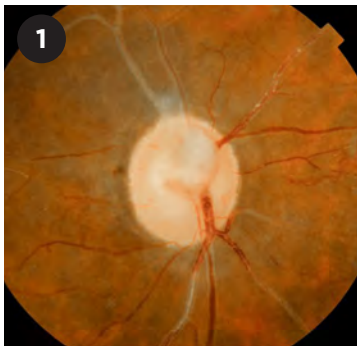
Hariprasad Vokuda, MD, Shree Hari Netralaya, Udupi, India

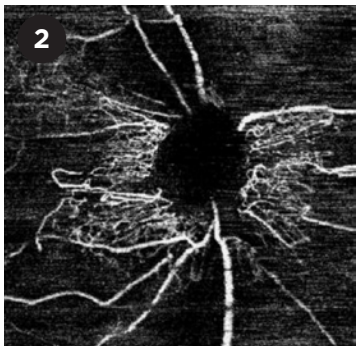


WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments and get the answer to last month's mystery.*

LAST MONTH'S BLINK

Central Retinal Artery Occlusion in Quiescent Diabetic Retinopathy





A 40-year-old man with a 15-year history of poorly controlled diabetes, hypertension, and dyslipidemia underwent bilateral vitrectomy and panretinal photocoagulation in 2015 for vitreous hemorrhages and proliferative diabetic retinopathy (PDR) in both eyes. He also had a cilioretinal artery occlusion in the left eye in 2016, which resulted in hand motions vision in that eye.

The patient was now complaining of acute and painless vision loss in the right eye for the past 15 days. Visual acuity had dropped from 20/40 to 20/100. Funduscopy of the right eye revealed nonperfusion of several retinal arterioles emerging from the optic disc (Fig. 1). Other features included quiescent PDR, optic disc pallor, and papillary involuted fibrotic neovessels. Arterial nonperfusion was also evident on optical coherence tomography angiography (Fig. 2), suggesting central retinal artery occlusion in the right eye.

WRITTEN BY **ANA FERREIRA, MD,** AND **RITA COUCEIRO, MD.** PHOTO BY **BRUNO PEREIRA, COT.** ALL ARE AT HOSPITAL VILA FRANCA DE XIRA, LISBON, PORTUGAL.

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