AMERICAN ACADEMY
OF OPHTHALMOLOGY®

EyeNet®

APRIL 2020

ZAP, LiGHT & SALT

Take Clinical Cues From These Three Glaucoma Trials

Concussion Care
Searching for Better Science

High-Tech, Mobile Perimetry
From Smartphones to VR

MORNING ROUNDS
A Case of Corneal Crystals

Protecting Sight. Empowering Lives.®

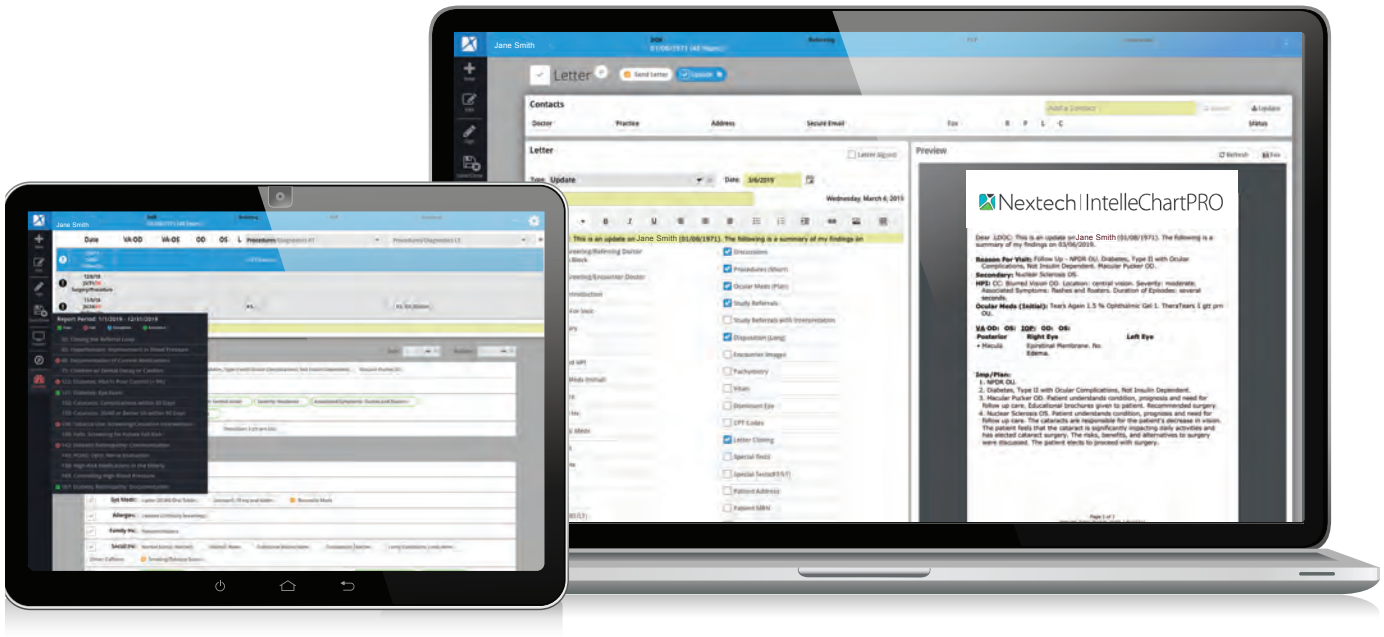
Nextech

Maximize Efficiency with the Most Intuitive Ophthalmology EHR

STREAMLINED
Regulatory Features

UNMATCHED
Provider Communications

OPTIMAL
Charting Speeds



IntelleChartPRO

#1 No. of Registered Practices

IRIS® Registry EHR Collaborator

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Experience Nextech at ASCRS Booth #841

(800) 868-3694 | Nextech.com/Ophthalmology

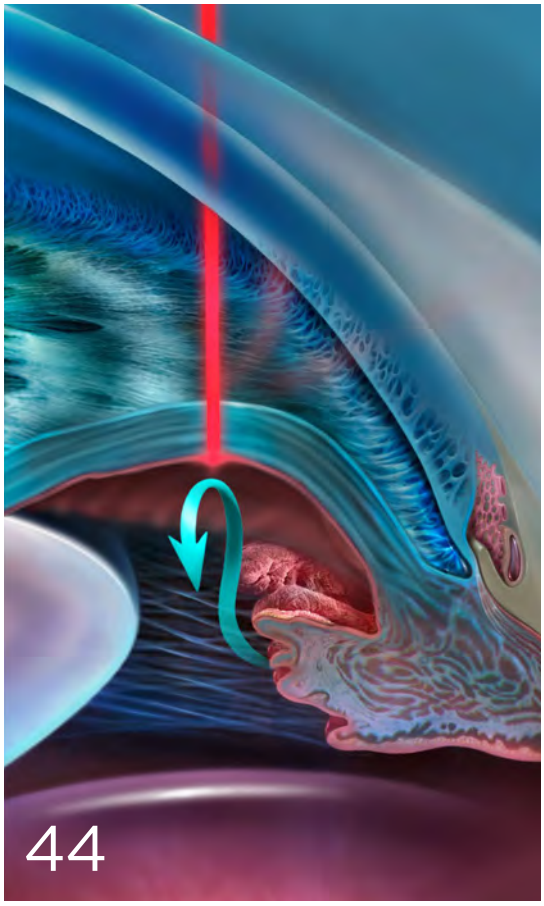
AMERICAN ACADEMY
OF OPHTHALMOLOGY®

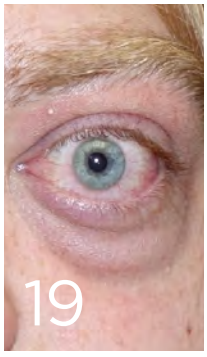
Only Academy Members Register for Free for the World's Premier Ophthalmic Meeting

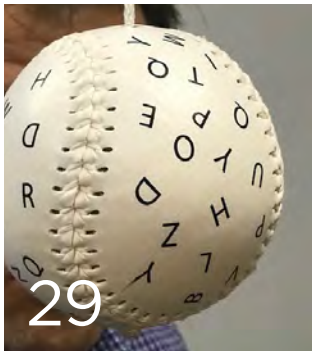
Only Academy members register for free for AAO 2020 (a $1,050 value). Envision the possibilities of tomorrow at the **Academy's annual meeting — Where all of ophthalmology meets®**. Showcasing cutting-edge technology and the best and brightest of our global community, it's an opportunity like no other to develop your network and skills.

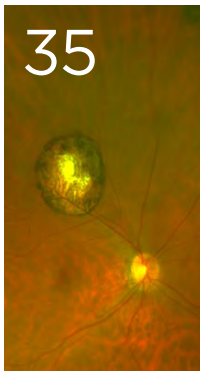
Renew your membership and activate the most valuable benefits in our profession. aao.org/benefits


Custom Pak®
SURGICAL PROCEDURE PACK
Alcon
CUSTOM PAK®
SURGICAL PROCEDURE PACK
YOUR PROCEDURE. OUR PRIORITY.
ALWAYS THERE. ALWAYS READY.
BECAUSE YOU DESIGNED IT THAT WAY.
Alcon prioritizes the thing you don't need to worry about, equipping you with complete surgical packs, customized for each surgeon. Alcon Custom Pak® ensures that you are ready for every procedure, every time.
Your focus is on patients. We make sure it stays that way.
SEE HOW WE DO IT AT
www.myalcon.com/custompak
Alcon
©2019 Alcon Inc. 09/19 US-CPP-1900006







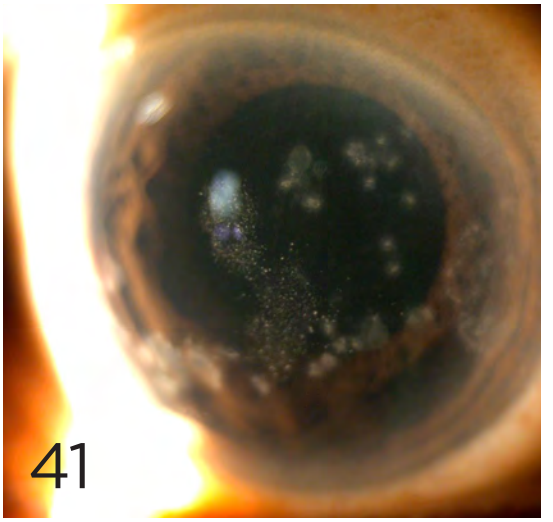


CONTENTS

APRIL 2020
VOLUME 24 • NUMBER 4

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 ILLUSTRATION
© 2020 Cynthia Turner

DEXYCU®
(dexamethasone intraocular suspension) 9%

The first and only FDA-approved, single-dose, sustained-release, intracameral steroid for the treatment of postoperative inflammation[1-3]

With a single injection at the end of cataract surgery, anti-inflammatory efficacy begins as early as day 1 and continues through day 30[1]*

- The percentage of patients who received DEXYCU® (dexamethasone intraocular suspension) 9% (517 mcg) who had anterior chamber cell clearing on day 8 was 60% (n=94/156) vs 20% (n=16/80) in the placebo group[1]
- The cumulative percentage of subjects receiving rescue medication of ocular steroid or nonsteroidal anti-inflammatory drug (NSAID) by day 30 was significantly lower in the DEXYCU (517 mcg) treatment group (20%; n=31/156) compared to placebo (54%; n=43/80)[1]

*DEXYCU was studied in a randomized, double-masked, placebo-controlled trial. Patients received either DEXYCU or a vehicle administered by a physician at the end of the surgical procedure. The primary endpoint was the proportion of patients with anterior chamber cell clearing (cell score=0) on postoperative day 8.

INDICATION AND USAGE

DEXYCU® (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure
- Prolonged use of corticosteroids, including DEXYCU, 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

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 corticosteroids

Exacerbation of Infection
- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of 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
- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and 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
- 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

Cataract Progression
- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

ADVERSE REACTIONS

- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

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

References: 1. DEXYCU® (dexamethasone intraocular suspension) 9% full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. December 2018. **2.** Donnenfeld E, Holland E. Dexamethasone intracameral drug-delivery suspension for inflammation associated with cataract surgery: a randomized, placebo-controlled, phase III trial. *Ophthalmology.* 2018;125(6):799-806. **3.** Data on file. EyePoint Pharmaceuticals, Inc.

EyePoint™ PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472

10/2019
US-DEX-1900208

DEXYCU (dexamethasone intraocular suspension) 9%,
for intraocular administration
Initial U.S. Approval: 1958

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

1 INDICATIONS AND USAGE

DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

Prolonged use of corticosteroids including DEXYCU 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.

5.2 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 corticosteroids.

5.3 Exacerbation of Infection

The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of 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.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires 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 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.

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.

5.4 Cataract Progression

The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Increase in Intraocular Pressure *[see Warning and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Infection Exacerbation *[see Warnings and Precautions (5.3)]*
- Cataract Progression *[see Warnings and Precautions (5.4)]*

6.1 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 following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively *[see Data in the full prescribing information].*

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use

Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use

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

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

CLINICAL EDUCATION

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Advance Your Patient Care with Practice-Ready Findings

Focus on proven conclusions that make a significant difference for your patients with *Focal Points*®.

This activity has been approved for *AMA PRA Category 1 Credit™*.

Each issue distills recent discoveries that are ready for you to integrate into your practice. Use the monthly **audio version** to conveniently earn **CME credits** and get up to speed while on the go.

Don't fall behind the curve. Subscribe at **aao.org/focalpoints**.

Protecting Sight. Empowering Lives.®

EDITORIAL BOARD

ACADEMY BOARD

Learn more about the Board *at aao.org/bot.*

EyeNet® MAGAZINE

David W. Parke II, MD
Editor-in-Chief

Ruth D. Williams, MD
Chief Medical Editor

Dale E. Fajardo, EdD, MBA
Publisher

Patty Ames
Executive Editor

Carey S. Ballard
Art Director / Production Manager

Chris McDonagh, Jean Shaw
Senior Editors

Miranda Smith
Associate Editor / Advertising Manager

Lori Baker-Schena, MBA, EdD; Leslie Burling; Peggy Denny; Miriam Karmel; Mike Mott; Linda Roach; Lynda Seminara; Annie Stuart; Rebecca Taylor; Gabrielle Weiner
Contributing Writers

Mark Mrvica, Kelly Miller
M.J. Mrvica Associates, Inc.
2 West Taunton Ave.,
Berlin, NJ 08009
856-768-9360
mjmrvica@mrvica.com
Advertising Sales

AMERICAN ACADEMY OF OPHTHALMOLOGY®
655 Beach St.
San Francisco, CA 94109
866-561-8558, 415-561-8500
aao.org

Governmental Affairs Division
20 F Street NW, Suite 400
Washington, DC 20001
202-737-6662

ARTICLE REVIEW PROCESS. Articles involving single-source medical and technical news are sent to quoted sources for verification of accuracy prior to publication. Quotes and other information in multisource articles are subject to confirmation by their respective sources. The chief medical editor and the executive editor review all news and feature articles and have sole discretion as to the acceptance and rejection of material and final authority as to revisions deemed necessary for publication.

DISCLOSURE KEY. Financial interests are indicated by the following abbreviations:
C = Consultant/Advisor
E = Employee
L = Speakers bureau
O = Equity owner
P = Patents/Royalty
S = Grant support
For definitions of each category, see aao.org/eyenet/disclosures.

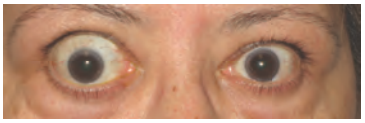
NOW APPROVED

The first and only FDA-approved treatment for Thyroid Eye Disease (TED)

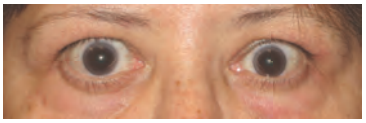
TEPEZZA™
teprotumumab-trbw

TEPEZZA decreases proptosis, diplopia, and the signs and symptoms of TED without concomitant steroids[1-3]

SEE THE DIFFERENCE[4]



BASELINE
Proptosis: 25 mm



POST-TREATMENT (WEEK 24)
Proptosis: 21 mm

Real TEPEZZA patient treated in a clinical trial. Results shown are with no surgical intervention. Individual results may vary. TEPEZZA met its primary endpoint vs placebo in 2 randomized, placebo-controlled trials (P<0.01), defined as proptosis responder rate at Week 24 (percentage of patients with ≥2-mm reduction in proptosis in the study eye from baseline).[1-3,5]

Learn more at TEPEZZAhcp.com

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Please see Brief Summary of Prescribing Information for TEPEZZA on adjacent pages.

References: 1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. **2.** Data on File. Horizon, April 2019. **3.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. **4.** Data on File. Horizon, January 2020. **5.** Data on File. Horizon, December 2019.

HORIZON

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions [see Warnings and Precautions]
- Exacerbation of Inflammatory Bowel Disease [see Warnings and Precautions]
- Hyperglycemia [see Warnings and Precautions]

Clinical Trials Experience

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

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase
c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor-1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There is insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss [see Data]. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA.

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

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

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breastfed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Inflammatory Bowel Disease

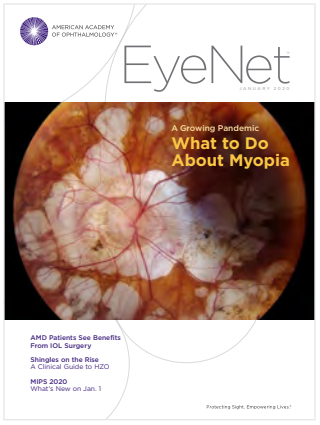
Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland
U.S. License No. 2022

Distributed by:
Horizon Therapeutics USA, Inc.
Lake Forest, IL 60045

HORIZON

Letters



Myopia in the South Pacific

I read with interest "What to Do About Myopia" (cover story, January). We have always seen more myopia in kids who spend most of their time reading, especially when there is a family history. (But this could be the result of myopia, rather than a cause.) The current increase in myopia and its progression seems to parallel the increase in the use of near vision for computer monitors, particularly with several daily hours on the small screens of personal phones. In our medical mission fieldwork throughout the South Pacific, we almost never see myopia, nor do we see personal cell phones.

John Corboy, MD
Mililani, Hawaii

Scope of Practice and Midlevel Providers

We would like to call attention to the Oct. 3, 2019, executive order by President Donald Trump: Protecting and Improving Medicare for Our Nation's Seniors. This order received very little media coverage, and we are afraid that many ophthalmologists are unaware of its far-reaching implications for medicine. While we support certain provisions of this order to preserve and improve Medicare, other components threaten the quality of care that patients will receive in the future.

Sections 5 (a), (b), and (c) of the executive order deal with midlevel providers (MLPs). These sections infer equivalency and interchangeability of the work done by physicians and MLPs. They call for the Secretary of Health & Human Services to develop regulations that would remove requirements for physician oversight of MLPs and equalize the reimbursement between physicians and nonphysicians.

In most states, the MLP works alongside a doctor who approves each medical diagnosis or treatment. This arrangement accommodates the limited medical knowledge and training of an MLP with direct physician supervision as a safeguard against patient harm. With the proper physician oversight, the MLP can play a very helpful role in our health care system. But to remove this supervisory requirement and to assume that MLPs can function as physicians is both erroneous and dangerous.

As a nation, we face more than a problem of access to health care. As our population ages, the complexity of medical problems increases dramatically, requiring treatment that is given, or directed, by a physician. The current disparity in reimbursement between physicians and MLPs reflects this complexity in care and the significant training required to manage complicated conditions competently and safely.

We feel that our political leaders, both at federal and state levels, are narrowly focused on expanding health care access without regard to the quality of that expanded care. Title V of President Barack Obama's Affordable Care Act allocates tens of millions of dollars to expand and promote MLP training programs. Between 2010 and 2016, MLPs made up 78% of all new health care practitioners in primary care.[1] The total number of licensed nurse practitioners in the United States is estimated to have doubled between 2007 and 2018, topping 270,000 in 2019.[2] This has not resulted in healthier patients, improved access to health care (most MLPs practice in already saturated areas), or decreased overall cost.

We must unite with our colleagues across specialties to stand against this misguided policy that puts patients, patient safety, and health care quality at risk. We must ensure that the independent practice of medicine and surgery remains the privilege of physicians.

Elan M. Newman, MD
San Diego, Calif.
Heather Chang, MD
South Pasadena, Calif.

1 Xue Y et al. *JAMA*. 2019;321(1):102-105.

2 www.aanp.org/news-feed/nurse-practitioner-role-continues-to-grow-to-meet-primary-care-provider-shortages-and-patient-demands. Published online Jan. 28, 2019.

Reply

The Academy thanks Drs. Newman and Chang for highlighting this important issue. The Academy works closely with the American Medical Association and the physician community to oppose inappropriate expansion of the scope of practice of optometrists and other allied health providers. In response to the October 2019 executive order, the Academy and more than 100 national and state physician organizations filed comments that echo those of Dr. Newman and Dr. Chang. The Academy will continue to join with the rest of the physician community to educate policymakers about the stark differences in education and training between physicians and nonphysicians; the value of supervision of allied health providers, such as advanced-practice nurses; and the importance of the Academy's surgery by surgeons efforts at all levels of government.

Rebecca Hyder
Academy Director of Federal Affairs
Washington, D.C.

Opinion

RUTH D. WILLIAMS, MD

Of Loss, Grief, and What Was Said

A few days ago, I greeted my longtime glaucoma patient with a routine question: "How are you?" She responded, "Not well. My son died on Thursday." We've all had patients who tell us about a major loss. But even though ophthalmologists are healers, we have little training in how to approach people who are grieving, and we mostly learn from experience.

In a *Chicago Tribune* editorial, Judith Weinstein (wife of retina specialist Mat MacCumber, MD, PhD) shared some helpful insights.[1] "Don't talk more than the bereaved," she counseled. Someone with a recent loss doesn't yet have the capacity to absorb others' experiences. And contain the urge to tell your own story. As my friend Beth Reece, who is manager of spiritual care at the Shirley Ryan AbilityLab in Chicago, put it, "Ask. Listen. Listen. Listen. Ask. Listen. Listen. Listen."

How can we invite a conversation? Beth, who works with patients in rehabilitation after a stroke, traumatic brain injury, severe burn, or limb loss, suggested simple open-ended questions, such as "How are you dealing with this?" And Judith advised against offering platitudes, such as "He's not suffering anymore" or "Your son wouldn't want you to be sad."

It's also not helpful to say, "I'm sorry for your loss." These phrases offer cheap—and ineffective—comfort. They reduce tension for the physician, they don't acknowledge the suffering of the patient, and they shut down the conversation. Consider, instead, a phrase that recognizes the patient's grief, such as "What a difficult time for you." This acknowledges the pain and doesn't try to fix or minimize it.

Giving advice isn't helpful, either. As with offering up platitudes, giving advice relieves the physician, but not the suffering patient, and it creates distance. As teacher and activist Parker Palmer wrote, "One of the hardest things we must do sometimes is to be present to another person's pain without trying to fix it, to simply stand respectfully at the edge of that person's mystery and misery."[2] As healers, we need to be comfortable with sorrow and check the surgeon's instinct to repair the pain.

After her teenager died from suicide, a friend explained that grief doesn't have a timetable, and that each of us accommodates to loss in our own way. From her I learned that it's helpful to remember the person who died, and now, many years later, I try to mention him in casual conversation. We can do the same for our patients. For a patient whose spouse had accompanied her to visits, I might say, "I can just see Mr. Jones sitting right there where he always sat," or "No one else can tell a joke like your husband could." These small comments honor the deceased and remind the patient that neither her husband, nor her grief, is forgotten.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

A now-retired retina specialist was legendary for taking meticulous "social notes" about his patients and would "remember" personal details about his patients, a practice that many physicians in our practice adopted. Our version of Epic has a yellow sticky note feature, which I use to remind myself to ask about the grieving process at the next visit. Patients genuinely appreciate hearing, "It's been just over a year since your husband died," or "How is the second year different than the first?" These are invitations to tell stories, a crucial component of the grieving process.

Ophthalmologists see a lot of patients in a session. The complexity of clinical care is increasing, and the competing demands can be exhausting. Do we really have time to add grief counseling into the busy clinic schedule? It really only takes a few minutes to ask a question and listen with full attention, and that just might be the most meaningful part of our day. Beth suggested that it's especially comforting when a physician breaks from a busy clinic to invite a story, creating an "in-between space." We are, after all, the healers.

1 Weinstein J. The art of consolation. *Chicago Tribune.* Jan. 16, 2020.
2 Palmer P. *Let Your Life Speak: Listening for the Voice of Vocation.* John Wiley & Sons; 2000:63.

100%
PRESERVATIVE FREE

ZIOPTAN®
(tafluprost ophthalmic solution) 0.0015%

ZIOPTAN.com

Cosopt® PF
(dorzolamide HCl - timolol maleate ophthalmic solution) 2% / 0.5%

COSOPTPF.com

AKORN

Current Perspective

DAVID W. PARKE II, MD

COVID-19 and Ophthalmology

As of the date this column was written (March 9), COVID-19 has been identified in 102 countries and community acquired disease has been documented in 35 U.S. states, and this will only increase. What are the implications for Academy members, their staffs, and their practices—and the Academy and its staff? How to be prudent and not panicked?

Ophthalmology has had a singular role in this pandemic. The 34-year-old Wuhan ophthalmologist Li Wenliang, MD, has been hailed in China as a hero for trying to alert authorities to the new virus and its dangers. He was accused by the local Public Security Bureau of "making false comments" that had "severely disturbed the social order" and told to stop. Dr. Li subsequently died of the disease.

The Academy as a science-based organization has been called upon to opine on numerous questions specifically relevant to our members and our profession. We are fortunate to have quite a few colleagues in our profession with special training and expertise in virology and/or public health epidemiology. The questions that they have fielded for the Academy have had to do with everything from disinfection to speed of spread to potential impact on our meetings.

Some of the information will continue to evolve as we all experience the global spread of the COVID-19 infection, its transmission, and its treatment. We've begun to understand that a large number of infected individuals remain asymptomatic or are minimally clinically symptomatic. And, specific to ophthalmology, we now recognize that conjunctivitis can be a presenting symptom and that slit-lamp exams (due to facial proximities) create a notable opportunity for transmission.

We now are realizing that the virus may have forever changed our world if it becomes (as some suspect it will) an annual outbreak. We may have to learn to live with it, much as we do with an ever-evolving flu season.

We have already learned not to make desperate purchases of N-95 masks for home use (sometimes at 200 times their usual cost). We will learn not to make draconian decisions about travel. And we may change our habits of human interaction—more fist and elbow bumps and fewer public kisses.

Our clinics and our offices (and the Academy itself) must consider creating plans, policies, and procedures to manage such issues as staff absenteeism due to issues with childcare, ill family members, shutdowns of mass transit, or personal illness. We may have shortages of medication or other necessities as global supply chains are interrupted. We will need to employ evidence-based disinfection protocols, isolate symptomatic individuals, and enact new travel and social distancing protocols. Throughout all of this, we should be guided by the science. The Academy's coronavirus webpage is updated regularly and is an excellent guide to resources pertaining to the outbreak and specifically ophthalmic practice: aao.org/coronavirus.

David W. Parke II, MD
Academy CEO

I have been asked how the Academy is handling this from a business perspective. Our policies and tactics are informed by science. As an example, we are not hoarding masks. We have encouraged staff not to wear them unless they are ill, and we have requested that all staff who are ill stay home and follow their physicians' advice regarding testing, self-quarantine, etc. We have emphasized not touching face, nose, and mouth and not using a hand to cover a cough or sneeze. We have educated on proper handwashing and on avoiding hand-to-hand contact. In other words, we are doing all the practical public health things that hopefully all our colleagues are reinforcing.

We also recognize that community-acquired disease may lead us to increase the amount of telecommuting to promote social distancing. We will, however, in such an eventuality, ensure that Academy services to members are uninterrupted.

Finally, about meetings: After the first draft of this article was posted online, based on best-available public health evidence, we postponed the Ophthalmology Business Summit and canceled the Mid-Year Forum. All of our decisions will be frequently reevaluated and guided by public health information. Our primary objective is the safety and well-being of our members. As for AAO 2020 in Las Vegas, we are very fortunate that it happens in mid-November. We should by that time be many months past the U.S. outbreak. I hope that it will be a time to celebrate 2020 The Year of Vision and share what we've learned from the tragic epidemic currently in our midst. Be well!

OMIDRIA now has a unique permanent J-code (J1097)[1]

Less stress, pure success ...in your O.R. day[2]

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.

The data are compelling and consistent—OMIDRIA makes cataract surgery better for you and your patients

Published and presented clinical data and manuscripts in preparation report that in post-launch (i.e., not included in current labeling), prospective and retrospective, double-masked and open-label, cohort and case-controlled, single and multi-center studies, the use of OMIDRIA statistically significantly:

- Prevents intraoperative floppy iris syndrome (IFIS)[3]
- Prevents iris prolapse[3]

Compared to steroids*:

- Reduces cystoid macular edema (CME)[4,5]
- Decreases breakthrough iritis[4]
- Reduces pain photophobia[4]

*OMIDRIA used intraoperatively with postoperative NSAIDs (no steroids) when compared to postoperative steroids with or without NSAIDs (no OMIDRIA).

Compared to epinephrine:

- Decreases complication rates[6]
- Decreases use of pupil-expanding devices (PEDs)[6-11]
- Enables performance of surgery and postoperative care without the use of steroids—allowing NSAID-only anti-inflammatory therapy[4,5,7]
- Shortens surgical times[6,7,9,10]
- Reduces need for opioids (i.e., fentanyl) during surgery while decreasing VAS pain scores[12]
- Prevents miosis during femtosecond laser-assisted surgery[11,13]
- Improves uncorrected visual acuity on day after surgery[6]

VAS = visual analog scale

OMIDRIA inhibits the release of inflammation-causing prostaglandins, preventing miosis and reducing postoperative pain[14]

OMIDRIA is separately reimbursed under Medicare Part B and by many Medicare Advantage and commercial payers.† Contact your OMIDRIA representative today or visit omidria.com to learn more.

†Based on currently available information and subject to change without notice. Individual plan coverage, payment, policies, and procedures may vary and should be confirmed by the facility. Omeros does not guarantee coverage or payment.

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigating solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

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

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.

References: 1. HCPCS quarterly update. CMS.gov. Available at: https://www.cms.gov/medicare/coding/hcpcsreleasecodesets/hcpcs-quarterly-update.html. Accessed August 9, 2019. **2.** Omeros survey data on file. **3.** Silverstein SM, Rana V, Stephens R, et al. Effect of phenylephrine 1.0%-ketorolac 0.3% injection on tamsulosin-associated intraoperative floppy-iris syndrome. *J Cataract Refract Surg.* 2018;44(9):1103-1108. **4.** Visco D, et al. Study to evaluate patient outcomes following cataract surgery when using OMIDRIA with postoperative topical NSAID administration versus a standard regimen of postoperative topical NSAIDs and steroids. Presented at: 28th Annual Meeting of the American College of Eye Surgeons (ACES), the American Board of Eye Surgery (ABES), and the Society for Excellence in Eyecare (SEE), Caribbean Eye Meeting; February 1-5, 2019; Cancún, Mexico. **5.** Walter K, Kauffman L, Hess J. Rate of pseudophakic cystoid macular edema using intraoperative and topical NSAIDs alone without steroids. Manuscript submitted for publication. 2019. **6.** Rosenberg ED, Nattis AS, Alevi D, et al. Visual outcomes, efficacy, and surgical complications associated with intracameral phenylephrine 1.0%/ketorolac 0.3% administered during cataract surgery. *Clin Ophthalmol.* 2018;12:21-28. **7.** Al-Hashimi S, Donaldson K, Davidson R, et al. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg.* 2018;44:1032-1041. **8.** Bucci FA Jr, Michalek B, Fluet AT. Comparison of the frequency of use of a pupil expansion device with and without an intracameral phenylephrine and ketorolac injection 1%/0.3% at the time of routine cataract surgery. *Clin Ophthalmol.* 2017;11:1039-1043. **9.** Visco D. Effect of phenylephrine/ketorolac on iris fixation ring use and surgical times in patients at risk of intraoperative miosis. *Clin Ophthalmol.* 2018;12:301-305. **10.** Matossian C, Teves N. Clinical outcomes of phenylephrine/ketorolac intraocular solution versus epinephrine in cataract surgery in a real-world setting. Manuscript submitted for publication. 2018. **11.** Walter K, Delwadia N, Coben J. Continuous intracameral phenylephrine-ketorolac irrigation for miosis prevention in femtosecond laser-assisted cataract surgery: reduction in surgical time and iris manipulation. *J Cataract Refract Surg.* 2019;45(4):465-469. doi: 10.1016/j.jcrs.2018.11.004. **12.** Donnenfeld E, Shojaei R. Effect of intracameral phenylephrine and ketorolac 1.0%/0.3% on intraoperative pain and opioid use during cataract surgery. Manuscript submitted for publication. 2019. **13.** Gayton JL. Effect of early phenylephrine and ketorolac injection 1% / 0.3% (Omidria®) usage on pupil diameter in traditional and femtosecond laser assisted cataract surgery. E-poster presented at: 15th International Congress on Vision Science and Eye; August 10-11 2017; London, UK. **14.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017.

OMIDRIA®

(phenylephrine and ketorolac intraocular solution) 1% / 0.3%

During ASCRS, Get Your FREE AB Max™

The POWER of the PULSE

Advanced Doctor Treatment for Anterior Blepharitis*

Visit Myco Industries/AB Max™ in Booth 466 During ASCRS

As part of the special program during the event, when you purchase six (6) boxes of AB Max™ procedure packs, you will get the AB Max™ device for FREE.

From one of the inventors of the first doctor's treatment for blepharitis — the AB Max™ is a new Doctor's Treatment for Anterior Blepharitis* with Patented PULSE functionality specifically engineered to remove even the most tenacious debris and plaque (biofilm) while gently massaging the outer eyelid margins for a better patient experience!

This innovative product delivers a newly Patented PULSE action for more efficient and rapid outer eyelid debridement, and a more comfortable patient experience without catching or pulling long eyelashes or lash extensions out.

AB Max™ provides:

- **BETTER treatment outcomes with HIGHER PROFITS**
- **Add $100,000 or more to your bottom line annually**
- **During the event - NO CAPITAL INVESTMENT required**

Ask us about our Trade IN Trade UP

to upgrade your first-generation device for the AB Max™

www.AB-Max.com • 1-800-721-8006

**Anterior blepharitis means blepharitis on the outer eyelid margin, including the eyelashes.*

AB Max™

OCULOPLASTICS

New Drug Targets Challenge of Thyroid Eye Disease

FOR THE FIRST TIME, A MEDICATION has been approved that can stop and modify the debilitating and sight-threatening pathology of thyroid eye disease. Teprotumumab (Tepezza) gained expedited approval from the FDA in January.

The drug is a fully human monoclonal antibody inhibitor of the insulin-like growth factor I receptor (IGF-IR), which orbital fibroblasts and B and T cells overexpress in Graves disease and thyroid eye disease (TED).[1]

TED "is really burdensome for patients. It impairs their vision, in addition to causing their facial disfigurement and double vision. Teprotumumab is the first medication that reverses all of those things, and with mild to moderate side effects," said Raymond S. Douglas, MD, PhD, one of the principal investigators in OPTIC, the study that led to the FDA's approval. "My patients are just thrilled. This has been a real game-changer."

OPTIC results. Earlier this year, researchers published results of OPTIC, a phase 3 trial.[2] In this study, 41 patients with TED received a total of eight intravenous infusions of teprotumumab, spaced three weeks apart. They showed significantly greater improvement in their disease at 24 weeks than did the 42 participants who received placebo.

The trial achieved its primary outcome—a reduction in proptosis of 2 mm or more—in 83% of the treated patients at 24 weeks. This compared to 10% in the placebo group ($p < 0.001$).

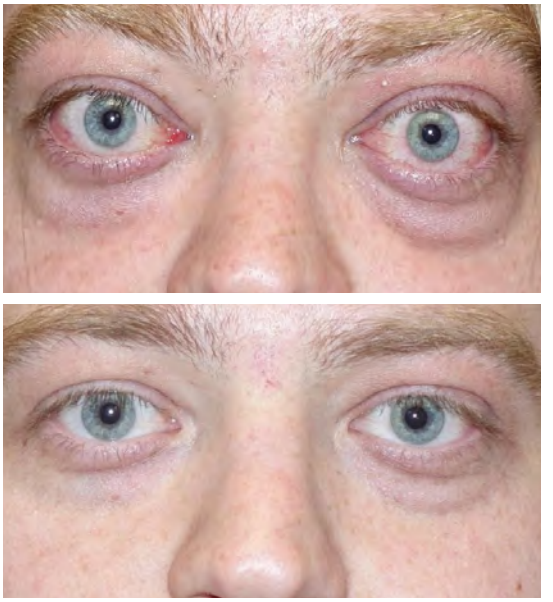
Early disease improvement. More than half of the treated patients (56%) reached this study marker in as few as six weeks, and they continued to improve through 24 weeks, said Dr. Douglas, at Cedars-Sinai Medical Center in Los Angeles.

Additional findings. The study also found significantly greater improvements in the treated patients' secondary outcomes ($p \leq 0.001$ for all), the researchers reported. These clinical measures included overall response (78% of treated patients vs. 7% of the placebo group); Clinical Activity Score of 0 or 1 (59% vs. 21%); the mean change in proptosis (−3.32 mm vs. −0.53 mm); and diplopia response (68% vs. 29%).

In addition, improvement was noted in a 16-item quality of life (QoL) questionnaire specific to Graves disease (mean change of 17.28 points in treated patients vs. 1.80 points in the placebo group). This self-administered questionnaire includes questions on visual and psychosocial functioning; a mean change of at least 6 points is considered clinically significant.

Side effects. Adverse events associated with the drug were mild to moderate in most cases and included muscle spasms (32%), alopecia (20%), nausea (15%), fatigue (12%), and diarrhea and headache (both 10%), the researchers reported. There were two serious adverse events: an infusion reaction that resolved with corticosteroid treatment, and pneumothorax that was considered unrelated to the drug.

Mechanism of action. Previous research has shown that teprotumumab blocks the pathologic immune responses of active TED by reducing signaling by both IGF-IR and thyrotropin receptors.[1] Unchecked, the activated receptors lead to the formation of physical and functional molecular complexes that trigger hyaluronan accumulation and expression of cytokines, which in turn cause inflammation, edema, and expansion of



EFFECT OF TREATMENT. *A patient with thyroid eye disease before and after treatment with teprotumumab. The drug was administered intravenously once every three weeks during the 24-week trial; evaluation of effectiveness is continuing beyond that point.*

Raymond S. Douglas, MD, PhD

extraocular muscle and adipose tissue, Dr. Douglas said.

It is not clear how long the drug's ability to inhibit the receptors will persist beyond 24 weeks, Dr. Douglas said. The drug manufacturer is conducting a postmarketing study intended to help clarify this issue, he said.

A new paradigm? Looking ahead, the approval of teprotumumab represents "a pivotal moment" in the treatment of TED, Dr. Douglas said. "I consider this a generational medication. I think our fellows who are training now will be hard-pressed to remember the times before teprotumumab came on the market for TED, much like the times before biologics came on the market for rheumatoid arthritis" and revolutionized treatment for that disease. *—Linda Roach*

1 Smith TJ, Janssen JAMJL. *Endocr Rev.* 2019; 40(1):236-267.

2 Douglas RS et al. *N Engl J Med.* 2020;382(4): 341-352.

Relevant financial disclosures—Dr. Douglas: Horizon Therapeutics: C.

PUBLIC HEALTH

Rapid Survey of Blindness: RAAB Method Accurate

RESEARCHERS LED BY A TEAM BASED in Hong Kong set out to assess the diagnostic accuracy of the survey method known as RAAB (for rapid assessment of avoidable blindness). They found that RAAB has high diagnostic accuracy for the detection of the prevalence of blindness, visual impairment (VI), and VI due to cataract.[1] "RAAB is a valuable alternative in areas where cost and logistical factors prohibit the use of conventional epidemiologic surveys," said coauthor Dennis S.C. Lam, MD, FRCOphth, at the Chinese University of Hong Kong.

A note on RAAB. This method is endorsed by the World Health Organization for population-based surveys of blindness and VI in people aged 50 years and older in a specific geographic area. Each RAAB survey involves an eye examination, with the use of a penlight, and a fundus exam via direct ophthalmoscopy. The exams are held in the participant's home. "The major advantages of this method are its simplicity, rapid conduct, lower cost, and use of standardized assessments," said Dr. Lam.

In the field. This study involved 2,145 people aged 50 years and older in 45 villages located in the Chaonan Region of southern China. All participants were examined according to the RAAB protocol; they were then offered a more extensive examination in a mobile eye clinic that was set up in a village center on the same day.

Exams in the mobile clinic included standardized visual acuity (VA) tests using logMAR charts, refraction, slit-lamp biomicroscopy, and a dilated fundus exam with a binocular indirect ophthalmoscope. Blindness and economic blindness were defined as having VA in the better-seeing eye of <20/400 and <20/200, respectively. VI was defined as having VA of <20/60 in the better eye. The primary cause of

REFRACTIVE

SMILE Approval Expanded

THE RESULTS OF A PIVOTAL CLINICAL TRIAL ARE OUT, paving the way for expanded FDA approval of small incision lenticule extraction (SMILE) for the correction of myopia and astigmatism.[1]

Since 2011, SMILE has evolved from a treatment for myopia to one for myopia with astigmatism up to –0.50 D—and now to one for correction of myopia with or without astigmatism up to –3.0 D. The flapless treatment, which reshapes the cornea using only a femtosecond laser, proved safe and effective and demonstrated predictable correction over the trial duration of 12 months, and patients achieved refractive stability between three and six months.

In the approved range, the procedure can be recommended to patients as an alternative method of refractive vision correction, said Jon G. Dishler, MD, at Dishler Laser Institute in Greenwood Village, Colorado.

The study. Between March 2015 and July 2016, 357 patients (357 eyes) underwent SMILE in one eye. (Most fellow eyes received excimer laser treatment.) Preoperative sphere ranged between –1.00 and –10.00 D, with manifest spherical equivalent (MSE) up to –11.50 D and refractive cylinder up to –3.0 D.

At 12 months, 95.3% of all eyes were within 0.50 D of emmetropia, 89.0% achieved uncorrected distance visual acuity (UDVA) of 20/20 or better, and 99.0% had UDVA of 20/40 or better. In addition, MSE went from –5.39 at baseline to –0.01 D, and average refractive cylinder went from –1.53 D to 0.18 D.

Complications. Three intraoperative events were associated with difficult lenticule removal and resultant cap tear. All resolved without sequelae at postoperative day one, and patients completed the study with UDVA of 20/20 or better. Eight adverse events occurred postoperatively; none had significant consequences.

Looking ahead. SMILE still does not address hyperopia, mixed astigmatism, or very high levels of astigmatism, Dr. Dishler noted. "But I would estimate that well over 90% of patients in search of refractive vision correction could be served by this procedure." He noted that the U.S. military is currently completing a SMILE study, and he added, "a procedure with rapid recovery without the limitations of a corneal flap is appealing to both patients and doctors." *—Miriam Karmel*

1 Dishler JG et al. *Ophthalmology*. Published online Jan. 14, 2020.

Relevant financial disclosures—Dr. Dishler: Carl Zeiss: C.

blindness and VI was defined according to the cause of VI in the participant's better eye.

Results. Of the 2,145 participants who were screened with RAAB, 327 (15.2%) refused to attend the mobile eye clinic, and two (0.1%) were unable to undergo the more in-depth examination.

Sensitivities ranged from 89.5% to 90.3%, and specificities ranged from 97.7% to 99.3% for detection of different levels of VI—and these results provide "strong support for the diagnostic accuracy of the RAAB methodology for the detection of blindness and VI," the researchers wrote.

With regard to blindness and VI owing to cataract and refractive error, RAAB was highly accurate for cataract but less so for refractive error.

Limitations. The authors noted that it is possible that their results overestimate the impact of cataract and underestimate those of glaucoma and posterior segment diseases on the prevalence of blindness and VI. Nonetheless, they said, the RAAB methodology "remains an important tool for informing research and policy for blindness prevention." *—Arthur Stone*

1 Zhang XJ et al. *Am J Ophthalmol.* Published online Dec. 14, 2019.

Relevant financial disclosures—Dr. Lam: None.

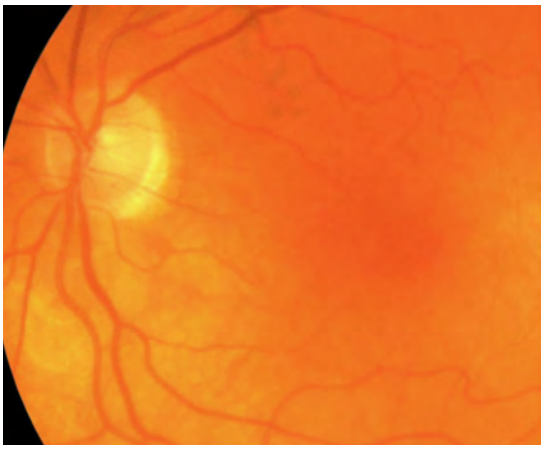
GLAUCOMA

Genetic Test Outlines POAG Risk Categories

A MULTICOUNTRY TEAM HAS DE-veloped a genetic test that stratifies individuals with glaucoma into risk groups.[1] The researchers' polygenic risk score (PRS), or genetic profiling strategy, determines how likely a patient is to develop primary open-angle glaucoma (POAG)—and indicates which patients should be offered early treatment and/or monitoring.

The PRS predicted that individuals in the top decile were at a 15-fold increased risk of advanced glaucoma and 21.5-fold increased risk of advanced high-tension glaucoma, relative to those in the bottom decile. What's more, those in the highest decile reached an absolute risk for glaucoma 10 years earlier than did participants at the bottom.

"Traditionally, genetic testing in glaucoma has focused on rare mutations such as the Gln368Ter variant in the *MYOC* gene. Our work provides the utility of mass screening," said Xikun Han, MSc, at the QIMR Berghofer Medical Research Institute in Brisbane, Australia. "Also, importantly, the prediction can be done before damage begins, and people who are stratified into the high-risk group can take the necessary precautions."



POAG RISK. *The risk calculator was found to be predictive of a number of factors, including earlier age of glaucoma diagnosis, increased likelihood of disease progression in early-stage disease, and greater need for incisional surgery in advanced disease.*

A new approach. Unlike existing risk calculators, which rely on general information such as age and intraocular pressure (IOP), the PRS is based on an individual's profile of all known risk loci for glaucoma. In this study, the researchers identified 107 new gene variants associated with glaucoma that increase the individual's risk of developing POAG.

To create the PRS, the researchers identified vertical cup/disc ratio risk variants from optic nerve photographs of 67,040 participants in the U.K. Biobank, which holds genotyping on 500,000 volunteer participants between the ages of 40 and 69. Thus, this investigation is the largest genome-wide association study of optic nerve morphology to date. In addition to information from the U.K. Biobank, they used other large biobanks to provide risk variants for IOP and POAG.

Age and family history mattered. The PRS, which could be approved for general use in one or two years, was significantly associated with age at POAG diagnosis. Individuals in the top 10% of PRS distribution were, on average, diagnosed seven years earlier than were those in the bottom 10%.

In addition, those in the highest decile had twice as many family members affected by glaucoma as did those at the bottom. Moreover, a higher PRS was associated with a greater need for trabeculectomy.

Room for improvement. The researchers noted that their risk calculator needs to be tested in other populations—and that it could be evaluated prospectively in a longitudinal intervention study. In an effort to improve the PRS' predictive power, the researchers hope to collect DNA from 20,000 people with glaucoma or a family history of glaucoma. "While a more accurate PRS is unlikely to move high-risk individuals to a low-risk category, the current PRS is less accurate for those in the moderately high-risk category," Mr. Han said. "An improved genetic test will help split up this group more effectively, enabling more precise guidance to be given to a larger number of people." *—Miriam Karmel*

1 Craig JE et al. *Nat Genet.* Published online Jan. 20, 2020.

Relevant financial disclosures—Mr. Han: None.

Xikun Han, MSc

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.

Make every second count with high-performance OCT.

ZEISS CIRRUS 6000

At 100,000 scans per second, ZEISS CIRRUS 6000 is the next-generation OCT delivering high-speed image capture with wider field of view and HD imaging detail.

Maximize patient throughput with **performance OCT, proven analytics and patient-first design.**

zeiss.com/CIRRUS6000

ZEISS

Seeing beyond

EN_31_030_0087I CIR.11579 Contact a local representative for regulatory status and approved labeling.

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Private Equity Trends in Eye Care

April 2020

Chen et al. set out to identify temporal and geographic trends in private equity (PE) acquisitions in eye care in the United States. They concluded that PE-backed acquisitions of ophthalmic and optometric practices have rapidly increased since 2012, with some platform companies having already been sold or recapitalized to new investors.

For this cross-sectional study, the authors used PE acquisition and investment data from Jan. 1, 2012, to Oct. 20, 2019. They identified 228 ophthalmic and optometric practices that had been acquired by 29 PE-backed platform companies during that time. Of the 228 practices, 127 were comprehensive/multispecialty practices, nine were retina practices, and 92 were optometry-specific practices; they were associated with 1,466 clinical locations and involved 2,146 clinicians.

Acquisitions increased rapidly between 2012 and 2019: From 2012-2016, 42 practices were acquired; this grew to 186 from 2017-2019. Financing rounds of platform companies paralleled temporal acquisition trends. Three platform companies, comprising 60% of platforms formed before 2016, were subsequently sold or recapitalized to new PE investors by the end of the study period, with a median holding period of 3.5 years. Acquisitions occurred in 40 states, with a majority of PE firms developing multistate platform companies.

Of note, the authors found a slight decline in acquisition numbers in 2019 and a lower rate of platform formations. They speculate that this decline in PE interest may be due to expectations of limited profit potential due to current health care and market trends. Finally, they emphasize that future research should assess the impact of short-term PE investment on patient, provider, and practice metrics. *(Also see related commentary by David W. Parke II, MD, in the same issue.)*

Eye Injuries in the Iraq and Afghanistan Conflicts

April 2020

In an effort to inform future military surgical training requirements and medical planning, **Breeze et al.** compared incidences, ocular injury types, and treatment performed on U.S. and U.K. military service members and host nation civilians within the Iraq and Afghanistan conflicts. They found that eye injuries were more likely to have been treated definitively in U.S. deployed military treatment facilities, reflecting the absence of ophthalmologists in their U.K. counterparts.

For this retrospective cohort study, the authors evaluated data on 67,586 patients in the U.S. and U.K. military trauma registries who were treated at deployed military treatment facilities between March 2003 and October 2011. An adjusted multiple logistic regression model was performed using the main outcome measures of enucleation or evisceration and primary open globe repair as dependent variables and casualty nationality, location, and the presence of an ophthalmic surgeon as independent variables.

Of the 67,586 patients, 5,719 (8%) had sustained eye injuries. Of these, the most common were open globe injury without intraocular foreign body (3,201; 56%). Adnexal injuries were recorded in 1,265 patients (22%). The odds of undergoing evisceration or enucleation for open globe injury was highest in Iraqi and Afghani civilians (odds ratio [OR], 9.23; $p < 0.001$), but there was no evidence of a difference between U.S. and U.K. military service member casualties ($p = 0.38$). Primary repair of open globe injury was more commonly undertaken at U.S. medical facilities (OR 5.71; $p < 0.0001$), reflecting the presence of an ophthalmic surgeon at the U.S. facilities.

The authors emphasized that their findings support the inclusion of ophthalmologists in deployed coalition treatment facilities during future conflicts.

Medication Adherence and Visual Field Progression in CIGTS

April 2020

The Collaborative Initial Glaucoma Treatment Study (CIGTS) compared the effect of initial treatment with topical medications to that of trabeculectomy in 607 patients with newly diagnosed glaucoma. Of these, 307 were randomized to the medication arm of the study and underwent regular assessment of their medication adherence and disease progression. **Newman-Casey et al.** reported long-term data on these patients; they found a statistically and clinically significant association between medication nonadherence and visual field (VF) loss.

The patients were followed up at six-month intervals for an average of 7.3 years. Medication adherence was assessed via telephone calls in which patients were asked, "We want to get an idea of what medication taking is like for you. Did you happen to miss any dose of your [name of medication] yesterday (yes or no)?" The impact of medication adherence on mean deviation (MD) over time was assessed with a linear mixed regression model adjusting for the effects of baseline MD and age, cataract extraction, interactions, and time (through year 8, excluding time after crossover to surgery). Medication adherence was modeled as a cumulative sum of the number of prior visits at which a missed dose of medication was reported.

Adherence data were available for 306 of the 307 patients. Of these, 142 (46%) reported never missing a dose of medication, 112 (37%) reported missing medication at up to one-third of visits, 31 (10%) reported missing medication at one-third to two-thirds of visits, and 21 (7%) reported missing medication at more than two-thirds of visits.

Worse medication adherence was associated with loss of MD over time ($p = 0.005$). For patients who reported never missing a dose of medication, the average predicted MD loss over eight years was 0.62 decibels (dB), consistent with age-related loss (95% confidence interval [CI], 0.17-1.06; $p = 0.007$). Patients who reported missing medication doses at one-third of visits had a loss of 1.42 dB (95% CI, 0.86-1.98; $p < 0.0001$), and those who reported missing medication doses at two-thirds of visits showed a loss of 2.23 dB (95% CI, 1.19-3.26; $p < 0.0001$).

The authors noted that 79% of participants had five years of follow-up data, thus offering unique insights into the association between medication-taking behavior and the progression of VF loss. —*Summaries by Arthur Stone*

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Predictors of Success in Selective Laser Trabeculoplasty

March/April 2020

In a large cohort of eyes undergoing selective laser trabeculoplasty (SLT), **Kuley et al.** sought to determine predictors of SLT success in lowering intraocular pressure (IOP) in patients with glaucoma. They found that greater pre-SLT IOP and angle pigment correlated positively with SLT success. Patient age, total SLT power, severity of glaucoma, and prior treatments were not associated with SLT success or failure.

For this retrospective case series, the authors evaluated 677 patients (997 eyes) who were treated at a single center by three glaucoma specialists between Jan. 1, 2012, and June 30, 2018. Baseline, demographic, procedural, and ophthalmic examination data were recorded at the time of the first SLT. IOP and medication data were recorded at all follow-up visits. SLT success was defined as IOP decrease greater than or equal to 20% from baseline at the three-, six-, and 12-month follow-up visits. Eyes were considered to have failed and were censored when additional SLT or glaucoma surgery was performed.

The patients' mean age was 70.2 (± 11.5) years. SLT success was achieved in 227 eyes (22.8%), while 770 (77.2%) failed to meet success criteria. Of the patients who did not achieve success, 523 failed due to insufficient reduction in IOP (<20% from baseline), and 46 failed due to requiring SLT or surgery. Pre-SLT IOP was 21.95 ± 5.2 mm Hg on 2.0 ± 1.2 medications in eyes with successful SLT, versus 19.0 ± 5.0 mm Hg ($p < 0.0001$) on 2.1 ± 1.3 medications ($p = 0.52$) in eyes with SLT failure.

At one year, mean IOP in eyes with SLT success was 14.7 ± 3.2 mm Hg on 2.0 ± 1.2 medications, compared to 16.3 ± 4.7 mm Hg ($p = 0.008$) on a mean of 1.9 ± 1.3 medications ($p = 0.37$) in eyes that failed SLT. Eyes with SLT success more often had greater angle pigment grading. There was no correlation between SLT outcomes and patients' age, glaucoma severity, total SLT power, type of glaucoma, visual field mean defect, or retinal nerve fiber layer thickness. —*Summary by Arthur Stone*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Long-Term Outcomes for Idiopathic Macular Holes

April 2020

Elhusseiny et al. set out to evaluate long-term structural and visual outcomes in patients who underwent pars plana vitrectomy (PPV) for idiopathic full-thickness macular hole (MH). They found that visual acuity continued to improve at least three years after PPV and was maintained thereafter in a substantial percentage of the patients.

This retrospective case series involved 80 patients (87 eyes) who underwent PPV for idiopathic MH and had follow-up of at least five years' duration. The mean postoperative follow-up was 9.6 ± 4.3 years (median, 9 years; range, 5-22 years). Only cases of idiopathic MH were included in this case analysis; patients with traumatic, recurrent, persistent, and secondary MHs were excluded. The main outcome measure was postoperative best-corrected visual acuity (BCVA) and its correlation with different parameters evident on spectral-domain optical coherence tomography (SD-OCT).

Initial successful MH closure was achieved in 82 eyes (94%). Seven eyes (8%) experienced MH reopening and underwent reoperation. The mean BCVA for the entire cohort improved

from 0.20 ± 0.13 before surgery to 0.39 ± 0.23 at one year, 0.43 ± 0.26 at two years, 0.47 ± 0.29 at three years, and 0.50 ± 0.26 at five years. In addition, for patients with longer follow-up, BCVA was 0.53 ± 0.28 at eight years and 0.61 ± 0.27 at 10 years.

SD-OCT confirmed that postoperative integrity of the ellipsoid zone was established in 52 eyes (60%) and external limiting membrane integrity was restored in 54 eyes (62%). Cystoid spaces of variable severity were observed in 28 eyes (32%). Pre-op BCVA of 20/60 or better and post-op ellipsoid zone and external limiting membrane integrity were associated with better BCVA at follow-up. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Corneal Hysteresis and Glaucoma Progression

April 2020

Wong et al. investigated the relationship between corneal hysteresis (CH) and displacement of the anterior lamina cribrosa surface (ALCS) in patients with glaucoma. They found that lower CH was associated with ALCS displacement over time, suggesting that it is a risk factor for glaucoma progression.

For this prospective observational case series, the researchers evaluated 96 patients (147 eyes) who either had glaucoma or were glaucoma suspects. The patients were followed for a mean of 3.5 years and 7.9 visits.

The researchers used the Ocular Response Analyzer (ORA) to measure CH and spectral-domain optical coherence tomography (SD-OCT) to assess mean ALCS depth and choroidal thickness. The rate of change in ALCS depth was calculated using linear mixed effect models.

Of the 147 eyes evaluated, 108 (73.4%) showed no significant ALCS displacement over time. However, 17 eyes (11.5%) showed posterior displacement, while 22 (15%) showed anterior displacement. Eyes with posterior displacement progressed more frequently than eyes with either anterior displacement or stable ALCS—and CH was significantly associated with a faster rate of posterior displacement during follow-up. Specifically, the researchers noted, for every 1 mm Hg decrease in CH, posterior displacement of the ALCS occurred at a rate of approximately 0.66 µm per year.

The results support the hypothesis that lower CH predisposes an eye to developing structural or functional glaucoma progression, the researchers said, as it serves as a marker for posterior ALCS displacement. Studies with a larger sample size and longer follow-up are needed.

Age at Time of Surgery for Intermittent Exotropia

April 2020

Repka et al. set out to determine the link between a child's age and the outcome of surgery for intermittent exotropia (IXT). They found that younger age at time of surgery is associated with better surgical outcomes.

For this secondary analysis of pooled data from a prospective randomized trial, the researchers evaluated 197 children between the ages of 3 and 11 (mean age, 6.2 years). All had basic-type IXT of 15 to 40 PD and at least 400 arcsec near stereoacuity. The children were randomly assigned to either 1) bilateral lateral rectus muscle recessions or 2) unilateral lateral rectus recession with medial rectus resection.

The results of this analysis revealed that the cumulative probability of having a suboptimal surgical outcome at the three-year post-op mark was 28% in children who were at least 3 but younger than 5 years old and approximately 50% for those who were age 5 or older. No other significant associations were found for other baseline factors, including magnitude of angle, control score, fixation preference, or near stereoacuity.

The authors caution that this analysis needs further confirmation from other studies. In particular, they said, the clinical question of whether early or delayed IXT surgery is associated with a better outcome needs to be addressed.

—*Summaries by Jean Shaw*

JAMA Ophthalmology

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

Treat-and-Extend With Ranibizumab: Two-Year Results

March 2020

In a randomized clinical trial, **Kertes et al.** compared the efficacy of monthly intravitreal injections of ranibizumab to that seen with a treat-and-extend (T&E) approach for choroidal neovascularization (CNV) secondary to neovascular age-related macular degeneration. They found that, through 24 months, the T&E regimen resulted in clinically meaningful improvement in best-corrected visual acuity (BCVA) that was not worse than that achieved with monthly treatment.

For this trial, the researchers enrolled 580 treatment-naive patients with CNV. Patients were randomized 1:1 to receive intravitreal ranibizumab 0.5 mg in either a T&E or a monthly dosing regimen. The main outcome measure was mean change in BCVA from baseline to month 24. By the two-year mark, 466 (80.3%) of the 580 patients had completed the study, as 49 patients (19.5%) withdrew from the T&E arm and 65 (21.8%) withdrew from the monthly treatment arm.

At month 24, results were as follows:

- For the primary outcome, the mean (standard deviation) change in VA was not worse in the T&E treatment group (6.8 [14.1] letters) compared with the monthly treatment group (6.0 [12.6] letters; difference, 0.9; 95% confidence interval [CI], –1.6-3.3; $p = 0.21$).
- At month 24, a lower mean number of injections was reported for T&E treatment (17.6) than with the monthly dosing regimen (23.5; difference, 5.9; 95% CI, 5.4-6.5; $p < 0.001$).
- In the T&E arm, 73.7% (95% CI, 67.6%-79.3%) of the patients were able to extend their treatment interval to eight or more weeks during the 24 months of treatment, and 43.1% (95% CI, 36.6%-49.8%) of the patients reached the 12-week maximum extension interval.
- In the T&E group, 42.9% gained 10 or more letters from baseline, while

25.5% gained 15 or more letters. In contrast, 36.4% in the monthly treatment group gained 10 or more letters, while 23.1% gained 10 or more letters.

- With regard to letters lost, 9.5% in the T&E group lost 10 or more letters, while 6.5% lost 15 or more letters. The rates were similar in the monthly treatment group, as 9.8% lost 10 or more letters and 5.8% lost 15 or more letters.

The study has been extended to 36 months, with all participants receiving ranibizumab on a T&E basis.

Metastasis in Uveal Melanoma

March 2020

When it comes to predicting metastasis in patients with uveal melanoma, how do The Cancer Genome Atlas (TCGA) and American Joint Committee on Cancer (AJCC) classification systems compare? **Mazloumi et al.** set out to answer this question and found that the TCGA provides greater accuracy.

For this retrospective cohort study, the researchers evaluated 642 patients with uveal melanoma who were treated with plaque radiotherapy from Oct. 1, 2008, to Dec. 31, 2018. Patients without complete genetic analysis of both chromosomes 3 and 8 were excluded, as were those with iris melanoma.

Using AJCC classification, the 642 tumors were classified into four categories, 17 subcategories, and four stages (based on tumor largest basal diameter, thickness, location, and extraocular extension). Based on genetic results, they were then grouped into four TCGA classes. The mean follow-up time for the entire cohort was 43.7 months (range, 1.4-159.2 months); the main outcome was the value of the two methods for predicting uveal melanoma–related metastasis.

The researchers used univariate Cox regression and multivariate models to predict the likelihood of metastasis. At five years, TCGA classification showed a higher value for prediction of distant metastasis in all models: With univariate analysis, the Wald statistic was 94.8 for four TCGA classes (hazard ratio [HR], 2.8; 95% confidence interval [CI], 2.3-3.5; $p < 0.01$) and 67.5 for four AJCC categories (HR, 2.6; 95% CI, 2.1-3.2; $p < 0.01$). With multivariate analysis, the Wald statistic for TCGA was 61.5 (HR, 2.4; 95% CI, 1.9-2.9; $p < 0.01$) and 35.5 for AJCC classification (HR, 1.9; 95% CI, 1.5-2.4; $p < 0.01$).

The authors noted that follow-up data of five or more years were available on only 168 of the 642 patients. Nonetheless, they said, when genetic testing results are available, the TCGA system may be a more accurate way to identify those patients who are at high risk of metastasis.

Genetics of Pigmentary Glaucoma

March 2020

Despite evidence of familial aggregation, the sporadic nature of pigmentary glaucoma (PG) and its status as a relatively rare condition have stymied research on heritability. **Simcoe et al.** set out to elucidate the genetics of PG by calculating its single-nucleotide polymorphism (SNP) heritability and identifying other genetic associations. They found a possible genetic component and shared genetic risks with iris pigmentation and myopia.

For this genome-wide association study, the researchers included 227 affected individuals from Germany and 291 control participants from the United Kingdom. All were of European ancestry. Those with PG were younger (mean age, 58.7 years) than the control participants (mean age, 80.2 years). Main outcome measures were an estimate of SNP-explained heritability for PG, correlations of effect sizes between PG and iris pigmentation and myopia, and correlations of effect sizes between PG and other eye phenotypes.

Results of the analysis showed a heritability estimate of 45% (standard error, 0.22; $p = 6.15 \times 10^{-10}$). Some SNPs that have previously been linked to eye pigmentation and myopia correlated with those for PG. However, PG appeared to be genetically distinct from primary open-angle glaucoma and its endophenotypes.

The results point to some possible mechanisms that may contribute to PG, and the authors called for further research. *—Summaries by Jean Shaw*

Other Journals

Selected by Prem S. Subramanian, MD, PhD

Optic Disc Drusen and NA-AION

Journal of Neuro-Ophthalmology
Published online Jan. 16, 2020

Rueløkke et al. compared the prevalence of known risk factors for nonarteritic anterior ischemic optic neuropathy (NA-AION) in patients with the condition and in a subset of those with optic disc drusen (ODD-AION). They found that ODD may be a risk factor in the development of AION.

The researchers evaluated 27 patients with NA-AION; all were originally treated between 2008 and 2017. For this case-control study, the patients were questioned about their medical history and were asked about general vascular risk factors (diabetes, hypertension, dyslipidemia, and smoking) and other risk factors for NA-AION (sleep apnea, anemia at time of diagnosis, and ocular surgery before diagnosis). The patients were imaged with optical coherence tomography with enhanced depth imaging (EDI-OCT) to confirm the presence or absence of ODD.

All told, 14 patients had no ODD, and 13 had ODD-AION. Four of the 13 with ODD-AION (31%) had vascular risk factors; in contrast, 12 of the 14 with no ODD (86%) had vascular risk factors. Five patients with ODD-AION (38%) had previous ocular surgery, versus one patient with no ODD (7%).

Of note, during EDI-OCT screening for this study, two of the patients were found to have buried ODD and were reclassified. This finding implies that not all otherwise healthy NA-AION patients had originally undergone thorough screening, the authors said, and they added that cases of ODD-AION may be underdiagnosed. In particular, they noted that optic disc edema during the acute stage of the disease can mask ODD on EDI-OCT, and they suggested scanning during follow-up.

—Summary by Jean Shaw

EXTRA **MORE ONLINE.** For an additional summary, see this article online at aao.org/eyenet.

SPEED, EASE, AND ACCURACY. IT'S ALL IN THE PLAN.

Introducing the ARGOS® Biometer with Image Guidance by Alcon®

An advanced comprehensive planning solution that delivers improved diagnostic precision and a more efficient clinical workflow. The ARGOS® Biometer combines speed, ease, and accuracy—seamlessly integrating best-in-class features that can provide better outcomes for your patients. Now that's great planning.

Alcon

ARGOS® with Image Guidance by ALCON® | Vision Planner

Concussion Care: Searching for Better Science

The number of diagnosed concussions in the United States is growing each year, with some conservative estimates of sports-related mild traumatic brain injury (mTBI) approaching 4 million annually.[1] The public's general awareness of concussions is also on the rise.

And that awareness is sparking some anxiety, said Rod Foroozan, MD, at Baylor College of Medicine in Houston. "We're seeing an increasing number of concerned patients blaming a multitude of symptoms on a concussion when, in fact, they're not at all due to a true brain injury."

Still more questions than answers. But despite this growing recognition of the sequelae of concussions and the latest developments in the field of traumatic brain injury, clinicians are often left with more questions than answers, said Dr. Foroozan. "Much of what we know about mTBI is more anecdotal than clinical. To provide the best care for patients suffering from a possible concussion, we need to start moving away from the subjective assessment of symptoms like headache or blurry vision and develop more objective testing."

On the Field

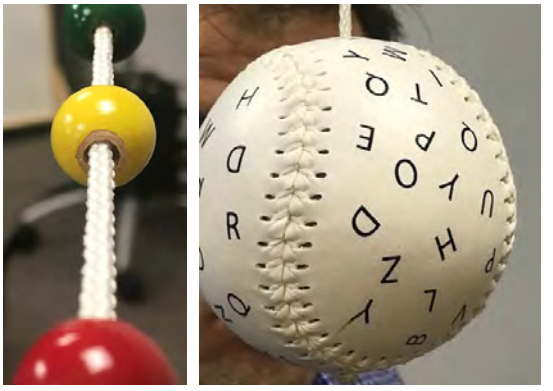
King-Devick. Over the past few years, one sideline protocol—the King-Devick (KD) test—has achieved a measure of acceptance. This test, which has potentially concussed athletes read numbers in quick succession (a method called rapid automatized naming), provides an objective measurement of the time needed to read numbers on a set of three cards. (The traditional test uses laminated cards, but a smartphone- or iPad-based version is also available.)

The success of the KD test lies in its ability to assess variance in saccades and other eye movements without the need for any specialized equipment. And the published data supports its use: A recent meta-analysis of 15 studies assessed the ability of the test to identify concussed athletes and concluded that rapid automatized naming is a critical dimension of mTBI testing.[2]

MULES. A similar test, the Mobile Universal Lexicon Evaluation System (MULES), also holds promise. This test uses a double-sided laminated card; participants are asked to identify photographs of multiple random objects as quickly as possible. Proponents of the MULES test cite its ability to take the KD test a step further by integrating color perception, object identification, conceptual representation, and articulation into a successful concussion assessment tool.[3,4]

Pros and cons. "These types of rapid automatized naming tests—the KD version, especially—are becoming the sideline standard because they are easy to manage, fairly objective, and supported by good research and evidence," said Prem S. Subramanian, MD, PhD, at the University of Colorado in Aurora. "But they also come with two inherent limitations: The tests require a good baseline, and they can be faked."

Need for baseline assessments. "Without a baseline assessment, the results of these tests following injury are of course meaningless because you have nothing to compare them to," said Dr. Foroozan, who also serves as the primary eye care provider for Houston's professional basketball and soccer teams. "So in the NBA, for example, you're seeing more and more teams have players take a KD test during the preseason—just like they would a baseline echocardiogram in case of a possible cardiac event during



MULTIFACETED APPROACH. *Adding vestibular therapy to visual therapy—shown here with (left) a Brock string and (right) a Marsden ball—can boost recovery.*

University of Colorado

BY MIKE MOTT, CONTRIBUTING WRITER, INTERVIEWING **ROD FOROOZAN, MD, JEFFREY R. HEBERT, PHD, PT,** AND **PREM S. SUBRAMANIAN, MD, PHD.**

the regular season."

Potential for fakery. However, baseline testing brings its own set of problems. "The innate problem with capturing a baseline is that an athlete can purposefully throw the test," said Dr. Subramanian. "Based on my experience with the National Collegiate Athletic Association, athletes realize there is a positive value in doing poorly on a preseason concussion assessment." That is, he explained, "If your baseline KD results are already near concussion level, you're less likely to be removed from a game later on after receiving a head injury."

Dr. Subramanian added, "We really need a sideline screener that is completely independent of subjectivity and athletes' intentions—something that can't be cracked."

In the Clinic

What about concussion testing outside of sports, where there is no baseline for comparison? "In the clinic, many ophthalmologists will see first-time patients with blunt trauma resulting from workplace or motor vehicle accidents, and this is where assessment becomes difficult," said Dr. Foroozan.

Without a baseline, Dr. Foroozan said, clinicians often depend on questionnaires. "For example, many concussion clinics place a heavy emphasis on patients' own assessment of symptoms." Sample questions on the questionnaires often include "How do you feel? Are you experiencing headache, light sensitivity, or blurred vision?" But as Dr. Foroozan noted, "These questionnaires really don't help us get a handle on which patients are experiencing true concussion injuries. They are too subjective."

Without an assessment that is weighted to objective criteria, clinicians are stumbling a bit in the dark, agreed Jeffrey R. Hebert, PhD, PT, at the University of Colorado in Aurora. "Subjectivity works both ways when we're trying to evaluate a patient's health." As he pointed out, some patients might overemphasize symptoms that they believe are related to an mTBI. In contrast, others might downplay their symptoms, risking their health to get back to work or resume other normal daily activities. "That's why we need an evaluation that is more quantifiable."

PUPILLARY EXAM. *Thanks to the search for objective biomarkers, quantitative pupillometry may replace the classic penlight exam.*

Hunting for Biomarkers

Are there any measurable structural changes to the eye that present following a traumatic brain injury? Although some studies have suggested changes in retinal thickness based on concussion history, nothing to date has clearly shown any structural ophthalmic biomarkers following an mTBI.[5] For example, a recent report comparing concussed patients and healthy controls found no significant difference between the two groups in full retinal thickness and only marginally significant reductions in the peripapillary retinal nerve fiber layer following injury.[6]

However, recent developments in eye tracking and pupillary reflex are demonstrating promise in this search for quantifiable concussion clues.

Eye tracking. "Our best diagnostic method for assessing mTBIs likely involves the automated measurement of eye movement abnormalities and saccadic velocity," said Dr. Subramanian. One research team recently evaluated an eye-tracking algorithm as a biomarker for concussion in children. They found that the velocity and conjugacy of eye movements correlated well with symptoms of mTBI and the resulting convergence and accommodative abnormalities.[7,8]

And industry is taking notice. For instance, Oculogica has used the research in this area to develop EyeBOX, a tabletop device that sends a small video around the perimeter of a rectangular screen and tracks each eye to gather 100,000 data points. The data are then fed into an algorithm to calculate a range of metrics quantifying speed, coordination, and range of motion. The result is a noninvasive aid for scoring the severity of a brain injury—and because the technology uses machine learning for statistical analysis, it doesn't require any baseline testing. (The EyeBOX received FDA De Novo approval on Dec. 28, 2018.)

The introduction of such technology "is proof that we can better quantify the functional capacity of ocular motor functions (for example, pursuit eye movements) following a possible mTBI," said Dr. Hebert. "And with it, we're getting closer to the type of objective assessment that can't be influenced at all by patients' self-reporting."

Pupillary reflex. Another possible biomarker involves quantitative pupillometry. "We're seeing more interest in the quantification of pupillary response and velocity not only when the eye is exposed to varying degrees of light but also in response to ocular motor functions such as convergence and divergence," said Dr. Hebert.

He added, "Unlike the use of a penlight for pupillary examination—which typically involves subjective interpretation—quantitative pupillometry can provide an objective, quantifiable method for evaluating patients with acute and chronic mTBI." Recent research, for example, has identified decreased pupil dilation, pupil constriction velocity, and pupil diameter along with increased pupil constriction latency in military personnel with blast-induced mTBI and high school football players following high-acceleration head injuries.[9,10]

Postconcussion Care

The search for better science is also key to better rehabilitation following a positive diagnosis.

Over the past decade, a number of concussion rehabilitation centers have

Shutterstock / Rocketclips

popped up across the country, driven in part by public anxiety over the dangers of mTBIs. The worst of these clinics provide services that have no scientific merit in an effort to capitalize on a new market, said Dr. Foroozan. The best, however, are utilizing the latest techniques in vision therapy and vestibular rehabilitation.

Yet as Dr. Hebert pointed out, too many clinicians continue to treat the visual and the vestibular as if they are mutually exclusive. "Academically and scientifically, we really haven't moved forward enough in terms of researching and quantifying the interplay between the visual symptoms that patients experience after mTBI and their accompanied vestibular and balance problems."

That's an important issue, Dr. Subramanian agreed. "One of the most overlooked aspects of vision is how we adjust the orientation of our body in space and maintain limb coordination." But that's not always front of mind for many clinicians who treat visual dysfunction following blunt injury trauma, he said. He added, "Many concussion symptoms are vague and challenging for clinicians to assess—dizziness, 'feeling off,' blurred vision. That's why we need more research into objectively measuring how a disturbance in balance and equilibrium can result in ocular motor abnormalities."

Integrated approach. Dr. Hebert has already seen the benefits of bringing the visual and the vestibular together in the rehabilitation of injured veterans. "Too often, a patient sees a vision therapist for one session and then a physical therapist for a separate session—the two are held in isolation," he said. "But in my experience, this isn't nearly as effective as a multifaceted approach."

In his clinic, he explained, "We'll use a Brock string for convergence insufficiencies and Marsden balls for smooth pursuit. But we also throw posture control into the mix." With this combination, "we're having patients work through their vision rehab at the same time that they work on their balance using head tips and roll maneuvers in standing. We're stimulating the vestibular system while seeing improvements with ocular motor challenges and resultant optic performance enhancement."

Looking ahead. It's this type of experimentation that will continue to push advances in postconcussion care, Dr. Subramanian said. "We're seeing a lot of debate as to the best methods of diagnosis and treatment. And the controversy arises because we simply don't have great standardized measures for many of the murky elements underlying the dysfunction that patients are reporting."

He concluded, "If we as clinicians really want to advance our understanding of mTBI, we have to look at the matter objectively; ask ourselves what makes sense, what doesn't, and what we haven't tried before; and design good clinical trials to establish the quantitative evidence that we are too often lacking."

1 Raghuram A et al. *Am J Ophthalmol.* 2019; 206:235-244.
2 Galetta KM et al. *Concussion.* 2015;1(2):CNC8.
3 Akhand O et al. *J Neurol Sci.* 2018;387:199-204.
4 Fallon S et al. *J Neurol Sci.* 2019;402:52-56.
5 Bixenmann B et al. *Int J Phys Med Rehabil.* 2014; 2:1-6.
6 Sabeti F et al. *Ophthalmology.* 2019;126(7): 1053-1055.
7 Bin Zahid A et al. *Clin J Sport Med.* Published online Aug. 8, 2018.
8 Howell DR et al. *Clin J Sport Med.* Published online June 21, 2018.
9 Capó-Aponte JE et al. *J Spine.* 2013. doi: 10.4172/2165-7939.S4-004.
10 Joseph JR et al. *J Neurosurg.* 2019;1-6.

Dr. Foroozan is associate professor of neuro-ophthalmology at the Baylor College of Medicine in Houston. *Relevant financial disclosures: None.*
Dr. Hebert is associate professor of physical medicine and rehabilitation at the Marcus Institute for Brain Health and director of the Physical Performance Laboratory at the University of Colorado Anschutz Medical Campus in Aurora. *Relevant financial disclosures: None.*
Dr. Subramanian is professor of ophthalmology, neurology, and neurosurgery; chief of neuro-ophthalmology; and vice chair for academic affairs for the department of ophthalmology at the University of Colorado Anschutz Medical Campus in Aurora. *Relevant financial disclosures: None.*

See disclosure key, page 10. **For full disclosures,** see this article at aao.org/eyenet.

6 reasons to switch to OMIC

EXPERIENCE
OMIC has defended far more ophthalmic claims than any other carrier. OMIC's knowledge and familiarity with regard to litigation targeting ophthalmology is unmatched in the industry.

EXPERTISE
OMIC is the only malpractice carrier offering comprehensive ophthalmic-specific education for physicians and their employees with resources designed to help minimize claims and lawsuits.

DEFENSE
OMIC has settled 25% fewer of the claims reported to us than our multi-specialty competitors and OMIC's average indemnity payment is 27% lower than the industry.

PERFORMANCE
OMIC is A (Excellent) rated by A.M. Best and has outperformed multi-specialty carriers in almost all financial benchmarks, including operating, combined and premium-to-surplus ratios.

BENEFITS
OMIC provides 17 regulatory and cyber coverage benefits in the standard malpractice policy at no additional premium.

DIVIDENDS
OMIC's operating advantage has made possible significantly higher policyholder dividends, averaging a 20.8% return per year during the most recent 5-year period compared to 6.6% for multi-specialty malpractice carriers.

OPHTHALMIC MUTUAL INSURANCE COMPANY

A Risk Retention Group of the
American Academy of Ophthalmology

Request a quote today!

Learn more at OMIC.com

Quick Quote:	OMIC.com/request-a-quote
Find Your Rep:	OMIC.com/about-omic/meet-omic
Resources:	OMIC.com/risk-management

Contact us:

800.562.6642

OMICPage MyOMIC

Perimetry Goes High-Tech and Mobile

Perimetry is a critical part of managing glaucoma, but traditional testing can present a challenge, especially for any patient who is unable to hold still long enough—or press the right buttons—for an accurate test. Moreover, the equipment used for standard automated perimetry (SAP) testing is costly and bulky.

Enter several novel platforms based on smartphone and virtual reality (VR) technology. As these high-tech, mobile systems are still in development, their eventual role has yet to be defined. For instance, will they replace SAP, or serve as an adjunct? Will they be used primarily in resource-poor areas? And what about individual home-based monitoring—or, at the other extreme, glaucoma screening in large populations?

Tracking Eye Movements

Eyecatcher, a tablet-based visual field (VF) test with a built-in eye-tracking camera, assesses how well a patient's reflexes respond to flashing lights onscreen.[1]

"When it comes to speeding up the way we can offer new therapies to patients, what we need is a very efficient way of measuring change in patients on a certain therapy," said David P. Crabb, PhD, MSc, head of the Crabb Lab at City, University of London (CUL), where Eyecatcher was developed. "One of the main aims of the Eyecatcher is to simplify how this measurement is done and make it more accessible."

When using the Eyecatcher, patients don't need to press buttons; they simply follow a spot of light on the tablet. The person's eye movements are then used to assess the VF. "It's not a replacement for current testing technology, but it does have potential as a case-finding or triage-type device to better direct resources toward people suspected to be at risk for loss of vision," Dr. Crabb said. The Eyecatcher also might allow clinicians to focus their energy and skills on treatment instead of screening. "One of our goals is to create a perimetry assessment that doesn't require glaucoma specialists," Dr. Crabb said.

FAST AND RELIABLE. *The smartphone-based PeekCS test offers an easy, rapid, and reliable way to test contrast sensitivity.*

Cost. "The traditional instruments that clinicians use cost $15,000 to $30,000, and we're offering a lower cost, more patient-friendly alternative," Dr. Crabb said. "Eyecatcher is a $400 tablet computer with a $100 eye-tracker camera."

Given the Eyecatcher's other advantages—small size, portability, and ease of use—it may well prove to be useful in low-resource communities. And Dr. Crabb believes that the Eyecatcher could be especially helpful in areas in which patients must pay for part of their care. "A challenging test is even more of a concern when patients have to pay [out of pocket] to perform a test they find very difficult to do," he said.

Next step: Home monitoring? CUL researchers also are researching the validity of home testing to gather accurate data, with patients taking Eyecatcher tablets home to test their own vision more frequently. "We've deliberately not supported them too much, other than giving them basic instructions, so next year we'll find out if they're actually using it or not," Dr. Crabb said.

"Home monitoring for people with glaucoma hasn't yet been studied with real scientific validity, such as discovering what patients actually do when you send them home with a new high-tech device," he noted. In a previous home monitoring study that used a web-based diary tool, a number of patients reported feeling anxious about their glaucoma, and one wanted to leave the study because it led to obsessive rumination about visual loss.[2]

"Glaucoma clinics are already very busy, which will get worse as the pop-

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **NIGEL M. BOLSTER, PHD, DAVID P. CRABB, PHD, MSC,** AND **RICHARD K. LEE, MD, PHD.**

Peek Vision Ltd.

ulation ages," Dr. Crabb said. "Home monitoring is likely to be better than eye exams once or twice a year, but we need to get the assessments and technology right. More research is needed to see if the benefits outweigh the monetary and clinical costs."

He added, "A lot of the tests we use in the clinic would benefit from being upgraded into technology we now have in our homes, such as smartphones and tablet computers."

Putting VR to Work

Another approach to VF testing involves a VR headset and a smartphone. This system uses frequency doubling technology (FDT), which is thought to stimulate the retinal ganglion cells most sensitive to glaucomatous damage.[3] A head-mounted VR display, a high-resolution smartphone, and a Bluetooth-enabled remote combine to run a mobile application based on the FDT C-20 screening protocol.[3]

"This screening device is part of the Portable Ophthalmologist Project (POP) at the Lee Lab to create portable, environment-hardened, low-cost technologies for vision screening and diagnosis that are critical for international and community ophthalmology in low-resource, remote, or large populations," said Richard K. Lee, MD, PhD, head of the Lee Lab at the Bascom Palmer Eye Institute in Miami. "The goal is ultimately an ophthalmologist's office in a backpack."

The device produces frequency doubling stimuli at 30 Hz with contrasts similar to the Humphrey Zeiss FDT.[3] In one study, testing on 19 eyes showed no significant difference in detecting glaucoma compared to the Humphrey Zeiss FDT; the authors suggested that primary open-angle glaucoma patients could be identified using a smartphone-based VR headset.[3]

Cost. This mobile virtual perimetry FDT device cost less than $130 to build. Patient data are stored locally on the smartphone or transferred to the cloud for integration into an electronic health record. An additional benefit: It can be used in areas without reliable electricity.

"This low-cost, portable technology is self-contained within a VR goggle and can upload data to the cloud in a HIPAA-compliant manner for longitudinal care in any type of environment around the world," Dr. Lee said. "It can also be used for handicapped patients who cannot sit in a regular station for formal VF testing, for ICU patients in bed, and for other patients with physical limitations or medical issues."

Testing Contrast Sensitivity

Another high-tech, mobile option for glaucoma screening: a smartphone-based contrast sensitivity (CS) test called the PeekCS.

"It's based on the PRCS (Pelli-Robson Contrast Sensitivity test), the gold standard for testing contrast sensitivity," said Nigel M. Bolster, PhD, with Peek Vision in London, developer of the PeekCS. "Currently, all of our global blindness metrics are based on measurement of distance visual acuity (VA), but that only tells part of the picture of a patient's vision." And although CS testing can help measure visual defects in glaucoma patients, it is infrequently measured in routine clinical practice.[4]

The PeekCS uses the Android OS with a "tumbling E" format. With a smartphone mounted on a tripod, the tester swipes the screen in the direction the participant pointed—a useful methodology for cross-cultural or low-literacy patients. The test was recently validated in a study of 147 patients with a mean age of 50.3 years (range, 18-82 years) who had been affected by trachoma.[4] The PeekCS measurements were highly correlated with those obtained with the PRCS test.

Why focus on contrast sensitivity? Dr. Bolster offered one scenario: "After cataract surgery, some patients receive a tiny increase in VA [postoperatively] and can't thank that doctor enough, whereas others come in and get a big increase in VA but aren't nearly as happy," he said. "We hypothesize that a lot of this is due to a lack of perceiving contrast."

An increase in the number of aging adults is expected to increase the number of cases of impaired CS due to glaucoma, macular degeneration, and diabetic retinopathy, even when patients have normal VA.[4] "We think CS testing, when combined with other low-cost tests, could be useful for detecting potential glaucoma cases and other degenerative eye diseases, and of great advantage in determining a more accurate view of quality of life based on a patient's vision," he said.

The overall goal? "We're seeking to address the looming global eye health crisis, with 2.2 billion people who have vision impairment or blindness worldwide," he said.

Additional VA test. The team has also developed a VA test called Peek Acuity. "We've been able to quickly train nonclinical staff to conduct the test with a high degree of accuracy and repeatability," Dr. Bolster said.

He added, "Peek Acuity has been classified as a Class 1 medical device and is available as a free download from the Google Play Store. It's part of a broader suite of technology-enabled tools and processes designed for eye care providers in remote and low-resource settings."

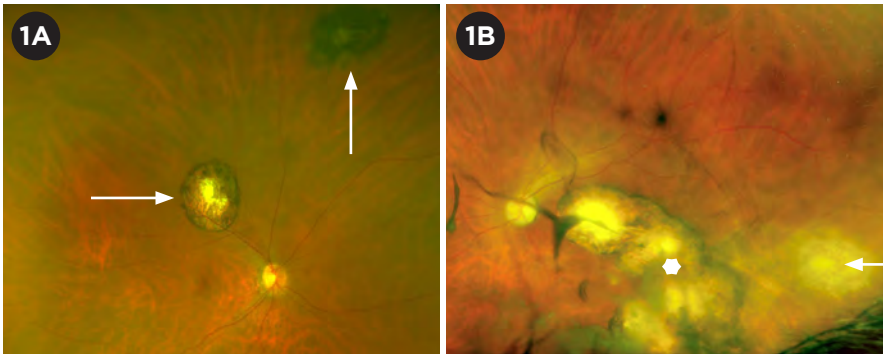
1 Jones PR et al. *Trans Vis Sci Tech.* 2019;8(1):17.
2 McDonald L et al. *J Ophthalmol.* 2017;2017:8452840.
3 Alawa KA et al. *Br J Ophthalmol.* Published online Sept. 17, 2019.
4 Habtamu E et al. *Trans Vis Sci Tech.* 2019;8(5):13.

Dr. Crabb is head of the Crabb Lab in the Division of Optometry and Visual Science at City, University of London in the United Kingdom. *Relevant financial disclosures: Fight for Sight: S.*
Dr. Bolster is head of product design and research at Peek Vision in London. *Relevant financial disclosures: Peek Vision: E.*
Dr. Lee is Walter G. Ross Distinguished Chair in Ophthalmic Research and associate professor of ophthalmology at the Bascom Palmer Eye Institute in Miami. He also holds secondary appointments in the Department of Cell Biology and Anatomy and in the Neuroscience Program at the University of Miami. *Relevant financial disclosures: None.*

See the disclosure key, page 10. **For full disclosures,** see this article at aao.org/eyenet.

MORE ONLINE. For another novel way to assess VF loss, see this article online at aao.org/eyenet.

Ocular Toxoplasmosis: A Refresher



ACTIVE AND INACTIVE LESIONS. *(1A) Widefield color fundus photograph shows inactive ocular toxoplasmosis lesions (arrows). (1B) Widefield color fundus photograph demonstrates an active ocular toxoplasmosis lesion with an area of fluffy white, focal necrotizing retinitis (arrow) adjacent to a large chorioretinal scar (star). Fundus appearance is hazy secondary to vitritis.*

Ocular toxoplasmosis, an infection of the retina and choroid caused by the intracellular parasite *Toxoplasma gondii,* is the leading cause of posterior uveitis worldwide and a common cause of vision loss resulting from intraocular infection. About 25% to 30% of the world's population is systemically infected with *Toxoplasma,* the most common foodborne parasitic infection globally.[1] Despite the global burden of disease, many patients infected with *Toxoplasma* may be asymptomatic or may present with nonspecific symptoms such as fever and generalized fatigue.[2]

The prevalence of systemic toxoplasmosis varies greatly by region. North America, Southeast Asia, and Northern Europe have a low prevalence (10%-30%), while a moderate prevalence (30%-50%) has been found in Central and Southern Europe. The prevalence of *Toxoplasma* infection is more than 60% in Latin America and tropical countries, with Brazil identified as having one of the highest rates.[1] Factors that may contribute to the elevated prevalence of toxoplasmosis in Brazil and other Latin American countries include a higher infection rate of animal reservoirs, greater concentration of parasite load in the environment, poor sanitary conditions, and host genetic factors.[1,2] Because ocular toxoplasmosis is a preventable form of worldwide blindness, understanding the pathophysiology and manifestations of the disease may lead to significantly decreased rates of infection.

Pathophysiology

Cats are the definitive hosts of *T. gondii,* while humans and other mammals are intermediate hosts. There are two major routes of transmission for infection. An individual may be infected by ingesting *Toxoplasma* oocysts in food or water contaminated by cat feces or by eating raw or undercooked meat containing tissue cysts within skeletal muscle.[2] Women who are infected during pregnancy have a high risk of transmitting the infection to the fetus, leading to devastating fetal complications including retinal infection, congenital malformation, and even fetal death.[3]

Congenital versus acquired. Congenital infection with *T. gondii* was formerly thought to be the most frequent cause of ocular toxoplasmosis. However, increasing evidence suggests that postnatal infection is actually more common, as many patients are diagnosed with ocular toxoplasmosis in adolescence.[2,3] Approximately one-third of toxoplasma chorioretinitis cases are caused by congenital infection and two-thirds by infection acquired later in life.[4] There is increasing evidence that parasite-specific as well as host-specific factors lead to development of ocular manifestations in some but not all individuals diagnosed with systemic toxoplasmosis.[5] Postnatal ocular toxoplasmosis has been shown to occur in 2% of individuals who are seropositive for the disease.[5]

Pregnancy. Congenital systemic toxoplasmosis develops in about 30% to 50% of infants whose mothers were

BY **NIKHILA KHANDWALA, MS,** AND **CAGRI G. BESIRLI, MD, PHD.** EDITED BY INGRID U. SCOTT, MD, MPH, AND BENNIE H. JENG, MD.

Department of Ophthalmology and Visual Sciences at the University of Michigan W.K. Kellogg Eye Center

first infected during pregnancy, with 70%-90% of infected neonates developing ocular manifestations. The risk of congenital toxoplasmosis is highest when infection occurs in the third trimester, with an approximately 72% chance of developing the disease at 36 weeks' gestation compared with a 6% chance at 13 weeks. Systemic manifestations are more severe if the infection presents within the first trimester.[3]

Histopathologic findings. Ocular toxoplasmosis is characterized by focal coagulative retinal necrosis and granulomatous inflammation of the choroid near the site of infection in the retina. Leukocytic infiltration may be noted in areas adjacent to the affected retina, as well as disruption of the retinal pigment epithelium with accumulation of pigment in areas of necrosis. Other findings associated with ocular toxoplasmosis include retinal neovascularization, retinal detachment, and optic neuritis.[3]

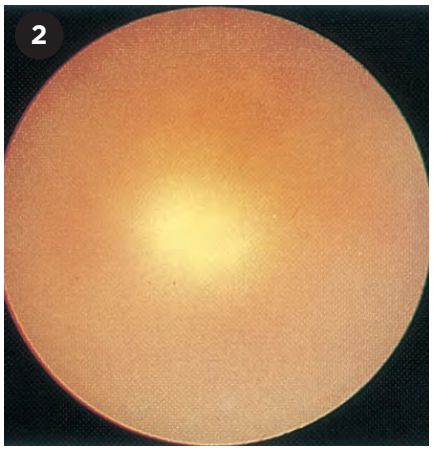
Clinical Features

Symptomatic ocular toxoplasmosis usually presents within the first two to four decades of life.[2]

Classic presentation. The typical finding of ocular toxoplasmosis is an area of fluffy white, focal necrotizing retinitis adjacent to a pigmented chorioretinal scar (Fig. 1). Vitreous inflammation may obscure the active lesion on dilated fundus examination, resulting in the headlight-in-fog sign (Fig. 2).

Other common signs of ocular toxoplasmosis include a satellite lesion (a new lesion adjacent to an inactive retinochoroidal scar), focal or widespread vasculitis, and inflammatory ocular hypertension. Patients often present with blurry vision secondary to vitritis, although some may be asymptomatic. Children with congenitally acquired ocular toxoplasmosis may present with cataract associated with retinochoroiditis. Up to 24% of patients have 20/200 vision or worse on presentation.[1]

Atypical presentation. Immunocompromised patients often present with a more aggressive form of the disease than those who are immunocompetent. Although immunocompromised patients may have some of the classic features of ocular toxoplasmosis, they may demonstrate atypical findings including multifocal retinochoroiditis, lack of vitritis, an active lesion larger than 2 disc diameters, absence of a retinochoroidal scar, bilateral ocular involvement, optic disc involvement, and retinal neovascularization.[1] Furthermore, immunocompromised individuals have a higher incidence of potentially fatal toxoplasmic encephalitis.[3]



A CLASSIC SIGN. *Vitreous inflammation may result in the headlight-in-fog sign.*

Recurrence. In most immunocompetent individuals, *Toxoplasma* cysts remain inactive within or near the retinal scar for a long period. Reactivation of retinitis usually occurs at the border of old scars, with the rupture of tissue cysts releasing organisms into the surrounding retina. The five-year recurrence rate was found to be 79%, and some patients have a propensity for multiple recurrences.[2] Patients who have undergone treatment for ocular toxoplasmosis have demonstrated a significant decrease in recurrence rate compared to those who did not receive treatment (6.6% vs. 23.8%, respectively).[1]

Diagnosis

Because most patients present with the classic features of a chorioretinal scar with a satellite lesion and areas of active retinochoroiditis, the diagnosis of ocular toxoplasmosis is often made on clinical presentation alone. However, if the clinical diagnosis is not definitive, laboratory tests and imaging may be helpful.

Laboratory tests. Serologic tests such as serum anti-*Toxoplasma* IgM and IgG are often obtained to confirm the diagnosis. Serum IgM and IgG antibodies are produced within one to two weeks after infection, with IgM levels rising in the first week and becoming undetectable within six to nine months. Nonreactive IgG rules out a diagnosis of toxoplasmosis in most immunocompetent individuals.

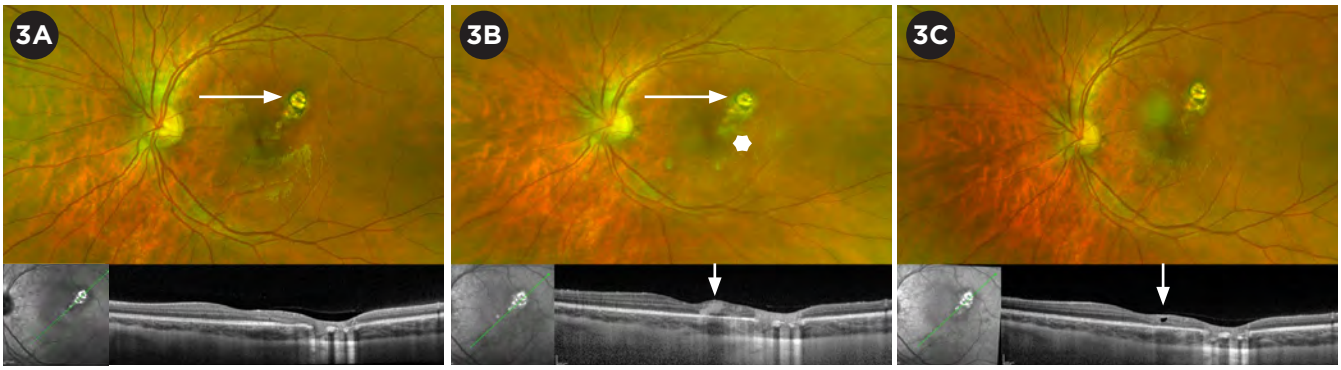
However, IgG and IgM levels should not be relied on for immunocompromised patients when there is high clinical suspicion for ocular toxoplasmosis; diagnosis should be based on clinical presentation along with other diagnostic tests, including ocular *T. gondii* antibody titers and polymerase chain reaction (PCR). Recently, PCR analysis of aqueous and vitreous samples has become available for diagnosis of ocular toxoplasmosis and may characterize various types of *T. gondii*.

Imaging. The use of spectral-domain optical coherence tomography has been shown to aid in the identification of the various stages of ocular toxoplasmosis. The active phase of the disease is characterized by disruption, thickening, and hyperreflectivity of the retina. With improvement of the disease, the hyperreflectivity resolves, leaving scarred lesions and retinal atrophy (Fig. 3).

Differential diagnosis. Several other diseases may feature focal necrotizing lesions similar to those of ocular toxoplasmosis, including viral retinitis, fungal infections, tuberculosis, and syphilis. Therefore, when the clinical presentation is not specifically diagnostic for ocular toxoplasmosis or when signs are seen in immunocompromised patients at high risk for opportunistic infections, serologic testing may be obtained to rule out other causes of infectious retinochoroiditis.

Management

There is no consensus on a treatment regimen for ocular toxoplasmosis. Most immunocompetent patients do not require medical treatment, as ocular toxoplasmosis is a self-limited disease that resolves spontaneously within four to eight weeks.[3] However, patients who



BEFORE AND AFTER. *(3A) Color fundus photograph shows an inactive ocular toxoplasmosis lesion in the macula (arrow). The optical coherence tomography (OCT) image below demonstrates a focal area of chorioretinal scarring and atrophy. (3B) Color fundus photograph taken two months later reveals an active ocular toxoplasmosis lesion (arrow) with adjacent fluffy white, focal necrotizing retinitis (star). Fundus view is slightly hazy because of mild vitritis. OCT showed corresponding full-thickness hyperreflectivity of the retina within previous area of infection as well as a new satellite lesion (arrow). (3C) Resolution of ocular toxoplasmosis following antiparasitic treatment. OCT below shows inner retinal cavitation and outer retinal collapse (arrow).*

present with reduced vision, those with lesions in vision-threatening anatomic areas, and immunocompromised patients are more likely to require treatment.

Classic treatment. The classic therapy for ocular toxoplasmosis consists of antiparasitic and anti-inflammatory medications, most commonly oral pyrimethamine and sulfadiazine, along with a systemic corticosteroid. However, the adverse effects associated with this regimen, notably leukopenia and thrombocytopenia, have led physicians to seek alternate effective therapies.[3]

Other approaches. A prospective multicenter study divided patients into three treatment groups: one receiving pyrimethamine, sulfadiazine, and corticosteroid; the second receiving clindamycin, sulfadiazine, and corticosteroid; and the third receiving trimethoprim-sulfamethoxazole and corticosteroid. It was reported that the most important determinant of the duration of ocular inflammation was the size of the retinal lesion itself, independent of treatment. The mean recurrence rate after three years was 49% for all patients, with no difference noted among treatment groups. The pyrimethamine group experienced the highest rate of side effects, which included thrombocytopenia and leukopenia.[6]

Patients with active ocular toxoplasmosis are often treated for a period of four to six weeks with either the classic triple-drug therapy of pyrimethamine, sulfadiazine, and corticosteroid or with trimethoprim-sulfamethoxazole monotherapy. If systemic treatment is contraindicated, intravitreal injection of clindamycin may be an alternative local treatment option.[7] Corticosteroids may be used in select cases to suppress inflammation and minimize chorioretinal damage associated with the host immune response against infection. The timing and dose of corticosteroids must balance suppression of the immune system with severity of the disease.[1]

Preventing recurrence. Individuals who have a history of frequent recurrence of ocular toxoplasmosis may benefit from long-term therapy to prevent subsequent recurrences. A study that randomized patients to long-term trimethoprim-sulfamethoxazole therapy versus placebo for a period of 20 months found a decreased recurrence rate in treated patients (6%) compared with untreated patients (23.8%).[8]

Conclusion

Ocular toxoplasmosis is the most common cause of infectious posterior uveitis and one of the leading causes of panuveitis worldwide. The prevalence of ocular toxoplasmosis varies based on geographic location. Diagnosis of ocular toxoplasmosis relies primarily upon clinical presentation, although laboratory testing and imaging may play a key role in atypical cases. Immunocompetent individuals may not need treatment because the disease typically regresses spontaneously within two months; however, patients who have vision-threatening lesions or are immunocompromised may require a combination of antiparasitic and anti-inflammatory treatment. Prompt recognition of atypical presentations and development of more efficacious therapies may prevent vision loss secondary to ocular toxoplasmosis.

1 Ozgonul C, Besirli CG. *Ophthalmic Res.* 2017;57(1):1-12.
2 Park YH, Nam HW. *Korean J Parasitol.* 2013;51(4):393-399.
3 Butler NJ et al. *Clin Exp Ophthalmol.* 2013;41(1):95-108.
4 Kijlstra A, Petersen E. *Ocul Immunol Inflamm.* 2014;22(2):138-147.
5 Pleyer U et al. *Ophthalmic Res.* 2014;52(3):116-123.
6 Rothova A et al. *Am J Ophthalmol.* 1993;115(4):517-523.
7 Soheilian M et al. *Ophthalmology.* 2005;112(11):1876-1882.
8 Silveira C et al. *Am J Ophthalmol.* 2002;134(1):41-46.

Ms. Khandwala is a fourth-year medical student at the University of Michigan. **Dr. Besirli** is an assistant professor in the Department of Ophthalmology and Visual Sciences at the University of Michigan W.K. Kellogg Eye Center. *Relevant financial disclosures: None.*

For full disclosures, see this article at www.aao.org/eyenet.

Department of Ophthalmology and Visual Sciences at the University of Michigan W.K. Kellogg Eye Center

START WITH THE POWER OF

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

As Demonstrated in Phase 3 Clinical Trials[1]

IMPORTANT SAFETY INFORMATION AND INDICATIONS

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

TRUST ≈8 YEARS of Extensive Clinical Experience and the Integrity of Data From Large, Well-Controlled Trials[1]

EYLEA IS THE

#1

PRESCRIBED anti-VEGF FDA approved for Wet AMD, DME, and MEfRVO*

*IBM Truven MarketScan data: Number of injections administered from Q4 2017 through Q3 2018; data on file.

AN ESTIMATED

≈9

MILLION doses administered to ≈790,000 eyes since launch (and counting)[2]

ACROSS ALL APPROVED INDICATIONS

8

PHASE 3 CLINICAL TRIALS including more than 3000 EYLEA–treated patients[1]

START WITH EYLEA

Visit HCP.EYLEA.us to see our data.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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

anti-VEGF = anti–vascular endothelial growth factor; AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; MEfRVO = Macular Edema following Retinal Vein Occlusion.

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

11/2019
EYL.19.10.0044

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments.
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure.
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events.
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

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

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

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

	CRVO		BRVO	
Adverse Reactions	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

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

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

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

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity.
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS.

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population 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 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

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

8.5 Geriatric Use.
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

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

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019
EYLEA® (aflibercept) Injection full
Prescribing Information.

EYL.19.07.0306

A Case of Corneal Crystals

Anne Eliott,* a 75-year-old African American retired nurse, visited us for her annual eye exam. She had a history of dry eye syndrome, cataract, and mild hypertensive retinopathy. She thought that her vision was slightly worse compared to last year, particularly in her right eye, and wondered if her cataracts could be the cause since she noticed more glare when driving at night.

Mrs. Eliott's medical history included well-controlled type 2 diabetes mellitus and hypertension. In addition, she was recently diagnosed with several other systemic disorders: seropositive rheumatoid arthritis, for which she was taking rituximab and leflunomide; anemia, thought to represent anemia of chronic disease from her rheumatoid arthritis; and osteoporosis. Her review of systems was positive only for pain in her hands, ankles, and back and numbness in her right hand.

What We Saw

When we examined Mrs. Eliott, her best-corrected visual acuity was 20/30 in her right eye and 20/25 in her left. In both eyes, pupillary examination was normal, visual fields were full on confrontation testing, ocular motility was normal, and intraocular pressure was 17 mm Hg. External examination was normal, but slit-lamp biomicroscopy revealed inferior punctate epithelial erosions and 1 to 2+ nuclear sclerotic cataracts in both eyes. Her dilated fundus examination was normal except for arterial attenuation and scattered peripheral drusen.

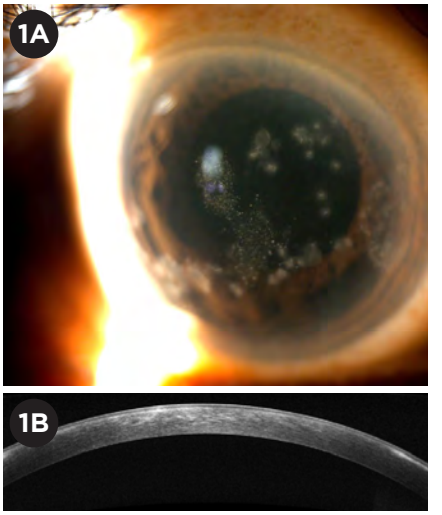
Unusual findings. In both corneas we observed central polychromatic, needlelike crystals in the anterior and mid stroma, with surrounding subepithelial nummular opacities (Fig. 1A). On optical coherence tomography (OCT), the opacities and crystals were hyperreflective (Fig. 1B).

We reviewed her chart and found that a note from a year prior mentioned a small area of crystalline changes in the right cornea at the 3-o'clock position. Her note from two years earlier was unremarkable.

Differential Diagnosis

Given Mrs. Eliott's age and the documentation of a normal ocular exam two years earlier, we put paraproteinemic keratopathy at the top of our differential. This condition is protean in its presentation and often initially misdiagnosed as lattice, granular, Schnyder, pre-Descemet, or gelatinous drop-like corneal dystrophy. It can also mimic cystinosis and lecithin-cholesterol acyltransferase deficiency and can even masquerade as interstitial keratitis, limbal stem cell deficiency, or Salzmann nodular degeneration.[1-3]

We reviewed her chart for lipid serologies, which were normal, arguing against Schnyder corneal dystrophy.



WHAT WE SAW. *(1A) Slit-lamp biomicroscopy and (1B) OCT revealed some unusual corneal findings.*

Additionally, Mrs. Eliott had no history of topical quinolone use or exposure to *Dieffenbachia* plants, both of which can cause crystalline keratopathies; nor did she have a history of penetrating keratoplasty, which would have raised suspicion for infectious crystalline keratopathy.

What the Tests Revealed

We ordered serum and urine protein electrophoresis, which revealed a monoclonal spike (M-spike), and immunofixation confirmed the presence of monoclonal IgG κ light chains. In conjunction with her primary care provider, we referred Mrs. Eliott to an oncologist, who performed a bone marrow biopsy, which revealed 7% plasma cells, and flow cytometry confirmed excess κ light chain reactivity

BY **KENNETH J. TAUBENSLAG, MD, DANIEL GEISLER, MD, ALEX MAMMEN, MD,** AND **JEAN C. HARWICK, MD, FACS.** EDITED BY INGRID U. SCOTT, MD, MPH.

UPMC Eye Center

without high-risk cytogenetics.

Positron emission tomography/computed tomography (PET/CT) was performed, showing fluorodeoxyglucose (FDG)-avid lytic lesions of the manubrium and L1 vertebral body (see Fig. 2 online at aao.org/eyenet). With normal renal function and serum albumin but elevated lactate dehydrogenase, she met diagnostic criteria for Durie-Salmon stage IIIA and Revised International Staging System stage II multiple myeloma. She underwent cytoreductive external beam radiation therapy for her lytic lesions before starting chemotherapy with lenalidomide and dexamethasone.

Discussion

The association between crystalline keratopathy and paraproteinemia was first described by Meesmann in 1934.[4] Immunoglobulin deposition in the cornea can occur in monoclonal gammopathy of unknown significance (MGUS), Waldenström macroglobulinemia, and multiple myeloma; less commonly, it may be associated with leukemia, lymphoma, cryoglobulinemia, and even intravenous immunoglobulin therapy. Among patients with known paraproteinemia, crystalline keratopathy is rare, occurring in only 1% of patients with MGUS.[5] Because prompt institution of chemotherapy or autologous stem cell transplant can improve survival for many patients with multiple myeloma, it is important for ophthalmologists to consider this diagnosis in elderly patients with new corneal opacification or crystalline deposits.

Pathophysiology. The pathogenesis of paraproteinemic keratopathy remains incompletely understood. It is seen most frequently in patients with κ light chain monoclonal gammopathies. Peripheral deposits are thought to diffuse from the limbal vasculature. Central deposits, on the other hand, are probably transported via the tear film and crystallize as the immunoglobulins encounter lower temperatures in the anterior stoma. Deeper deposits are speculated to diffuse from the anterior chamber and may be more likely to arise in the setting of endothelial pump dysfunction.[3]

Presentation and patterns. Because the clinical presentation is highly variable, paraproteinemic keratopathy poses a diagnostic challenge. Bilateral crystalline deposits in any layer of the cornea with surrounding patch-like opacities is the classic presentation.

However, Lisch et al. described paraproteinemic keratopathy as "chameleon-like" and proposed the following nomenclature to describe five possible morphologic patterns of corneal involvement: crystalline-like, lattice-like, peripheral granular-like, peripheral band-like, and peripheral patch-like.[1]

Diagnosis. Diagnostic testing should begin with a complete blood count with differential, serum and urine protein electrophoresis with immunofixation, and serology for cryoglobulinemia. If serology or urine studies demonstrate an M-spike, the patient should be referred promptly to an oncologist for a bone marrow biopsy and skeletal survey.

Many cases are also diagnosed by corneal biopsy, and electron microscopy is particularly useful. The ultrastructural appearance of the crystalline deposits can be as diverse as the clinical presentations. If biopsy reveals hollow, tubular crystalline deposits measuring 32 to 50 nm in diameter, the condition is termed immunotactoid keratopathy, owing to the similarity of the corneal deposits to the immunoglobulin deposits that are seen in immunotactoid glomerulopathy.[3]

Treatment. Paraproteinemic keratopathy is usually visually asymptomatic. For patients with visual symptoms, topical corticosteroids may be tried, but the results are often disappointing. Corneal transplantation can be performed for severe cases, but the crystalline deposits can recur in the graft.

Recently, several cases were described that improved with systemic chemotherapy, but data are limited on the efficacy of systemic chemotherapy for the keratopathy.[2] Of note, patients who carry a diagnosis of paraproteinemic keratopathy secondary to MGUS should follow up at least annually with an oncologist, as up to 20% of these patients will convert to multiple myeloma over the course of their lifetime.[1]

Our Patient's Course

We started Mrs. Eliott on topical 1% prednisolone acetate, twice daily in both eyes. After one month, she had no improvement in her crystalline keratopathy, and we discontinued the medication. She continued to complain of glare; so we performed cataract surgery, and the glare improved significantly. Further, after four cycles of chemotherapy, her paraproteinemic keratopathy resolved, although she achieved only a partial response systemically. At her most recent follow-up, she refracted to 20/20 in both eyes and was happy with her vision.

Conclusions

Paraproteinemia should be considered in the differential for any new corneal opacification in an adult. The diseases associated with paraproteinemic keratopathy can be life threatening, and timely diagnosis can facilitate early intervention and may improve survival. Mrs. Eliott's corneal findings demonstrate the classic appearance of this rare condition, though the clinical presentation is highly variable. This case demonstrates that, in some patients, the keratopathy resolves with systemic chemotherapy, and observation may be reasonable prior to recommending more invasive procedures such as corneal transplant.

*Patient name is fictitious.

1 Lisch W et al. *Cornea.* 2012;31(1):55-58.
2 Milman T et al. *Ophthalmology.* 2015; 122(9):1748-1756.
3 Garibaldi DC et al. *Surv Ophthalmol.* 2005; 50(1):61-80.
4 Meesman A. *Ber Dtsch Ophthalmol Ges.* 1934; 50:311-315.
5 Bourne WM et al. *Am J Ophthalmol.* 1989; 107(2):192-193.

Dr. Geisler is a pathology resident, and **Dr. Harwick** and **Dr. Mammen** are both cornea specialists; all three are at the University of Pittsburgh School of Medicine in Pittsburgh. **Dr. Taubenslag** is a retina fellow at Vanderbilt Eye Institute in Nashville, Tenn. *Financial disclosures: None.*

EXTRA **MORE ONLINE.** For PET/CT imaging (Fig. 2), see this article at aao.org/eyenet.

GET THE ADVANTAGE OF SPEED

OPHTHALMOLOGY'S FASTEST EHR & PM ALL-IN-ONE SOLUTION

GUARANTEED TO INCREASE YOUR EFFICIENCY

and Bottom Line in less than ***90 days!***

Our ***Advantage SMART Practice***® EHR and practice management solution uses real-time data to make every part of your workflow faster.

EHR | PM | ASC | RCM | MIPS

MyEyeStore | OPTICAL | PATIENT ENGAGEMENT | ON-LINE BILL PAY | ON-LINE SCHEDULING

2020 ASCRS ANNUAL MEETING. BOOTH #1241.

WWW.COMPULINKADVANTAGE.COM/ONETAB | 805.716.8688

compulink

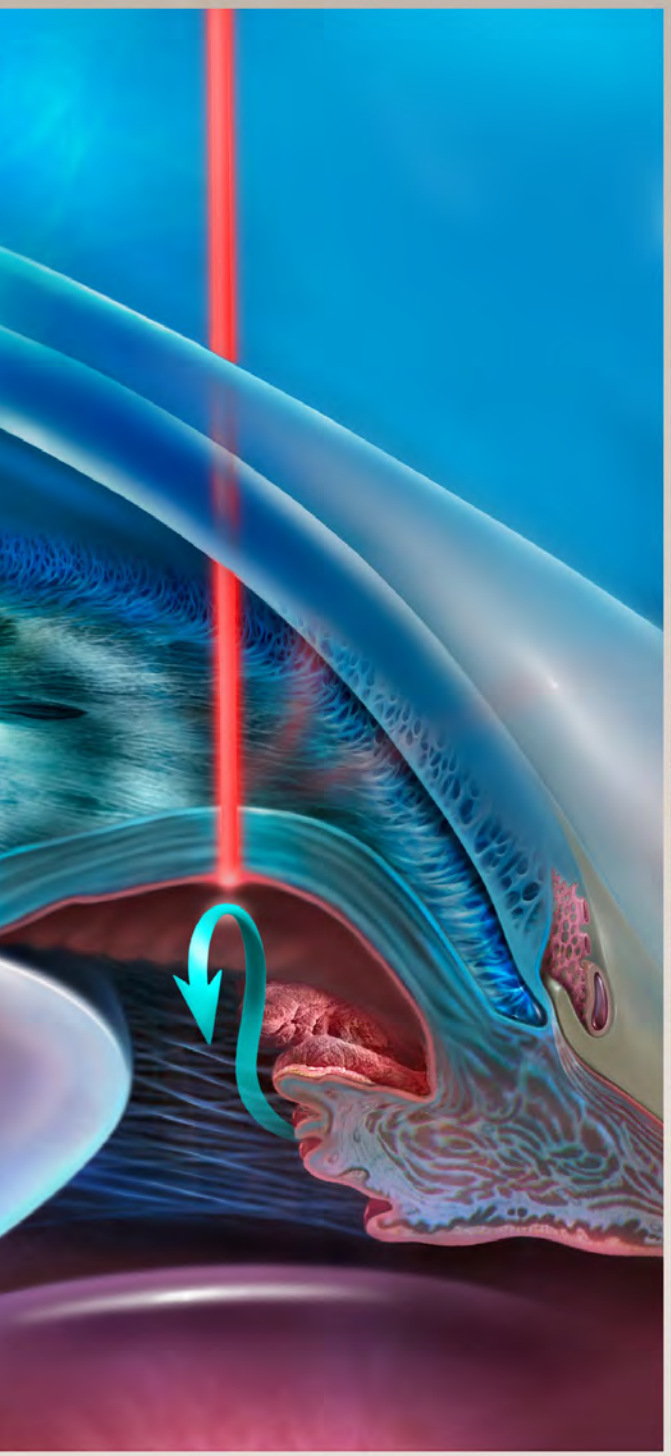
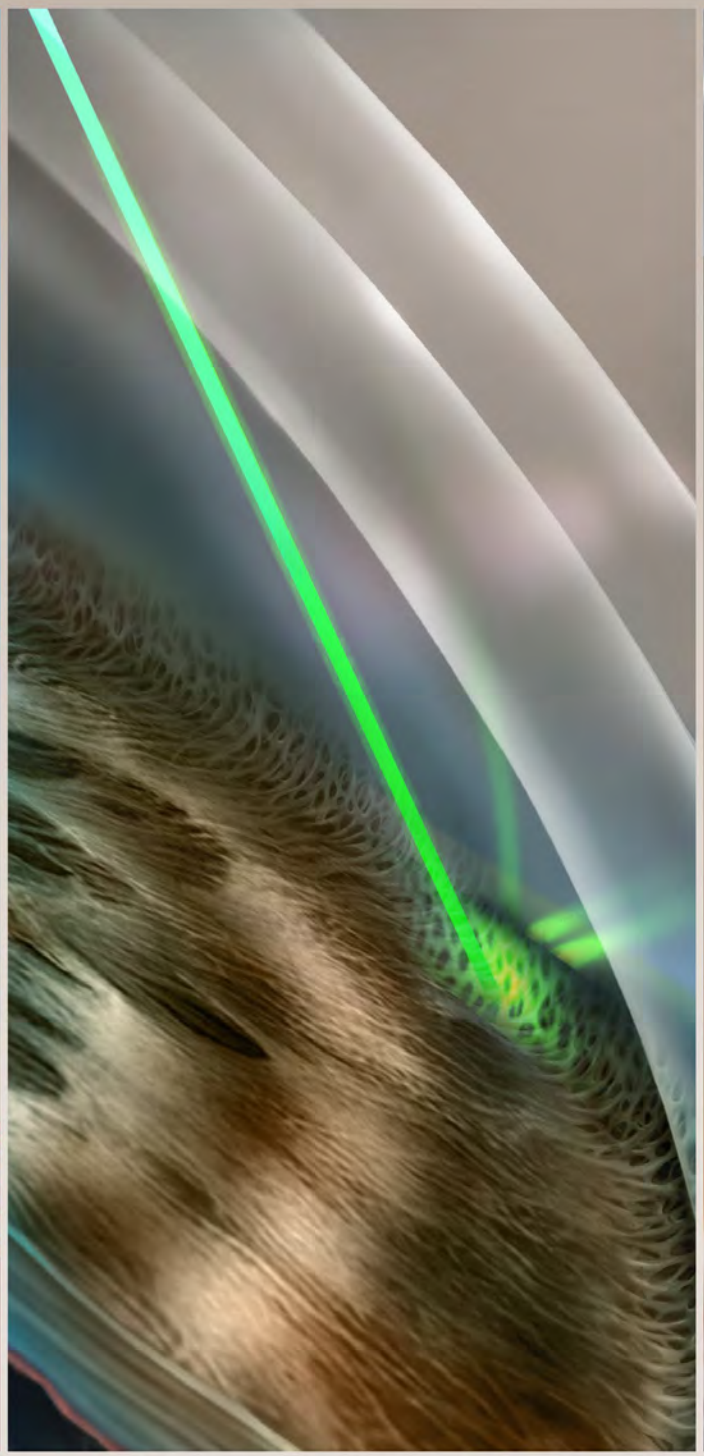




Illustration © 2020 Cynthia Turner

ZAP, LiGHT & SALT

Three recent studies address long-standing questions in glaucoma, and they may change your practice.

By Annie Stuart, Contributing Writer

Should prophylactic laser peripheral iridotomy (LPI) be used extensively for primary angle-closure suspects (PACS)? Are eye drops and selective laser trabeculoplasty (SLT) comparable first-line treatments for primary open-angle glaucoma or ocular hypertension? Is inflammation helpful or a hindrance after SLT?

In 2019, three glaucoma studies—ZAP, LiGHT, and SALT—addressed these very issues.[1-3] "We're lucky to have some high-quality studies on questions that are hard to answer," said Jo Ann A. Giaconi, MD, at the University of California, Los Angeles. "Whether simply confirming what we already thought to be true or exploring new areas, they're very helpful," added L. Jay Katz, MD, of the Wills Eye Glaucoma Service in Philadelphia.

ZAP: Prophylactic LPI for Primary Angle-Closure Suspects

In the early 1900s, researchers found that an iridectomy could relieve acute attacks of high pressure in eyes of patients with narrow-angle glaucoma, said David S. Friedman, MD, PhD, MPH, at Harvard Medical School in Boston. Ophthalmologists also performed this procedure in the fellow eye, which had a very high chance of getting an acute attack, he said.

Laser peripheral iridotomy. In the mid-1970s, LPI became the first-line treatment for primary angle-closure glaucoma. With the advent of laser, the risk-benefit ratio favored treatment over observation, so LPI also became a common treatment for patients with narrow angles, said H. George Tanaka, MD, at Vold Vision in Fayetteville, Arkansas. These primary angle-closure suspects have an increased risk of an acute attack but have healthy nerves, normal intraocular pressure (IOP), no peripheral anterior synechiae (PAS), and no other symptoms.

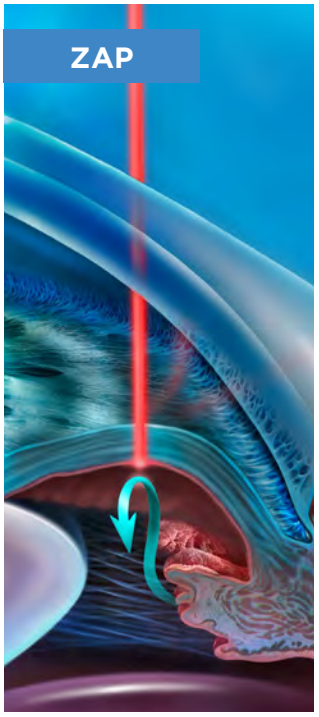
"We're always balancing risks and benefits with patients," said Dr. Katz. "What's the worst-case scenario if you develop angle-closure glaucoma? Pretty awful." On the other side of the coin, "What's the worst-case scenario with an iridotomy? A little inflammation, bleeding, or corneal edema, usually temporary," he said. Although less common, the main long-term problem is glare. "Out of an abundance of caution, we've been erring on the side of doing an LPI because you just never know," said Dr. Giaconi, adding that the risk of angle-closure glaucoma is higher for patients who don't follow up regularly.

The downside of this approach? There have been no guidelines or clinical evidence to support using LPI for all primary angle-closure suspects, said Dr. Tanaka. "That's why studies like ZAP are so important."

ZAP study design. In this six-year, randomized controlled trial, bilateral PACS patients between 50 and 70 years old were enrolled at a tertiary specialized hospital in Guangzhou, China. Eligible patients received LPI in one randomly selected eye, with an untreated contralateral control.

The primary outcome was PAC disease, a composite of three different endpoints: an increase in IOP, PAS, or acute angle closure. "In untreated eyes, PAS was by far the most common," said Dr. Friedman, a ZAP coauthor. "But PAS is a slow, benign process that doesn't result in visual loss or affect the patient's life if pressures remain normal."

Fewer attacks than expected. This study reaffirmed that acute angle closure is less common in at-risk eyes than previously thought and that the rate of developing PAS and elevated IOP is relatively slow, said Dr. Giaconi.



"Most attacks occurred after dilation," said Dr. Friedman, "which was a part of our protocol to allow observation of any impact iridotomy had on the development of cataract. Without dilation, only two cases of acute attacks occurred in nearly 900 untreated eyes followed for six years."

Older studies. "A similar earlier study reported nearly three times the rate of acute attacks," said Dr. Friedman. "We based our sample size on the assumption of more events, which just didn't happen." Why the difference? One possible reason, said Dr. Giaconi, is that the ZAP study screened many patients in the community instead of at tertiary clinics, where patients who show up may already have subtle signs and symptoms such as headache.

Another reason could be that past definitions of PACS and PAC have lacked precision, said Dr. Tanaka. And studies have used different criteria for occlusion, measured by gonioscopy, a somewhat subjective assessment resulting in variations in grading, added Dr. Katz.

Risk-benefit ratio: a new view. This study revealed that you needed to treat 44 PACS patients to prevent one case of primary angle closure in six years, said David Garway-Heath, MD, MBBS, FRCOphth, at Moorfields Eye Hospital in London. "One would imagine you'd need to treat even more to prevent one significant case of visual loss as a consequence of primary angle closure."

The conversion rate was much lower than previously reported, said Dr. Tanaka. "This really supports the notion that observing low-risk primary angle-closure suspects is usually fine. Conversely, treating all primary angle-closure suspects with laser iridotomy is definitely overtreatment."

LPI risks. As for LPI risks, the findings were mostly confirmatory, said Dr. Giaconi. In addition to assessing the more common side effects, the researchers also specifically looked at the endothelial cell count of the cornea, which didn't change, said Dr. Friedman. The study also didn't find an increased risk for cataract progression, but at least one other study[4] has, said Dr. Tanaka, who has also seen this in his practice.

Study strengths and limitations. Dr. Giaconi called ZAP a very strong study, but she would have liked to see data on the measurement of lens vault, which is a risk factor for pupillary block and acute angle attacks in other Asian studies. Overall, she said, "The researchers really thought about their inclusion and exclusion criteria and how to gather data." The study also verified endpoints with a second observer, said Dr. Friedman.

Dr. Tanaka pointed to three major strengths of the study: 1) Each patient served as his or her own control. 2) Follow-up was six years—extended to recruit more patients because the number of endpoints met at three years was so low. 3) All patients essentially received a provocative test: dilation.

The main limitation of the study is the inability to generalize results to other populations. "Angle closure in China may not be the same as in the United States, for example," said Dr. Katz, citing

When to Do LPI

Consider LPI in patients who have the following:

- symptoms such as headaches or eye pain that suggest the onset of primary angle closure,
- a family history of angle closure,
- signs such as PAS, high IOP, or an anterior lens surface that vaults into the anterior chamber.

Or those who may need dilated exams for diabetes and/or may not follow up or may travel to remote areas.

different demographics and eye anatomies, and potentially different mechanisms of action. On the plus side, Dr. Friedman doesn't think the rates would be higher elsewhere. That's because Chinese have among the highest rates of acute attacks.

"Along with others in the United Kingdom, the Working Group for the Royal College of Ophthalmologists will make recommendations for how to implement the results of this study in our population," said Prof. Garway-Heath. And the Academy's updated *Preferred Practice Patterns* for glaucoma are expected to be published in early 2021.

Practice implications? "ZAP has made me think that I don't want to search for angle-closure suspects because I'm not sure we benefit tremendously by finding them," said Dr. Friedman. "From a public health standpoint, I think we should change what we are doing."

Dr. Katz agrees that the public health message is clear, and that it's reassuring most people will be fine, even if never diagnosed. "But I'm a physician, and once I have a patient with a narrow angle in front of me, it's my obligation to describe the risks, options, warning signs of acute angle closure, and need for follow-up. Then it's the patient's right to decide what to do."

However, this study makes it easier to reassure primary angle-closure suspects that observation is often a reasonable approach, said Dr. Tanaka. "If you don't have LPI, your actual risk of an acute attack is on the order of 1% or less over six years." Dr. Tanaka would only recommend a laser iridotomy in a subset of patients, specifically those who:

- have symptoms such as headaches or eye pain that suggest the onset of primary angle closure,
- have a family history of angle closure,
- may need dilated exams for diabetes, and/or
- may not follow up or may travel to remote areas.

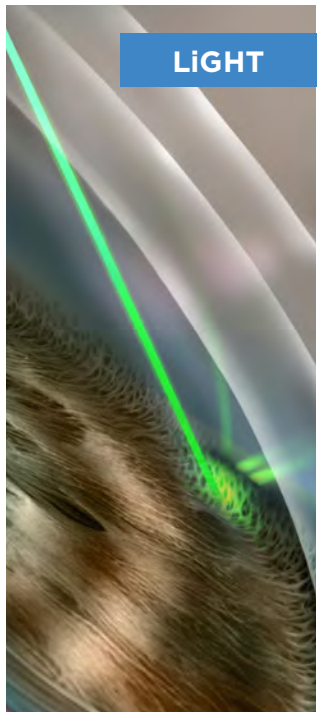
In addition, Dr. Giaconi recommends an iridotomy for patients with signs such as PAS, high IOP, or an anterior lens surface that vaults into the anterior chamber.

LiGHT: SLT or Eyedrops as First-Line Treatment

In 1990, the multicenter, NEI-funded Glaucoma Laser Trial evaluated argon laser trabeculoplasty (ALT), a predecessor to selective laser trabeculoplasty (SLT).[5] "The large study showed that it [ALT] was equally, if not more, effective than timolol in controlling the pressure in patients with glaucoma," said Dr. Katz, "but it never really changed our practice."

Smaller trials leading up to LiGHT showed similar results with SLT: It worked as well as latanoprost as a first-line therapy to lower pressure with minimal side effects, he said. But still there was little movement away from drops. "About 15 years ago, our Medicare billing study[6] showed that SLT was being done in less than 5% of people with glaucoma," said Dr. Friedman.

An eyedrops bias? Why the continued reluctance to use SLT? There are likely many contributors, ranging from provider inertia to patient fears and misconceptions. "When you say 'laser' to patients, it can conjure up James Bond being cut in half," said Prof. Garway-Heath. "Some clinicians also refer to laser as surgery. We tend not to in the United Kingdom, lumping it in with medical, rather than surgical, treatment."



Although the literature has made a fairly compelling case for laser trabeculoplasty as a first-line treatment, Prof. Garway-Heath said it's often been reserved as an add-on treatment in patients who have IOP that's been difficult to control with medication. "And in general, add-on treatments are less effective than primary treatments," he said, indicating that this may be an important reason laser has been perceived as having low efficacy in the real world.

Not only is SLT less effective when used as an add-on treatment, said Dr. Katz, but these patients are more likely to experience pressure spikes, inflammation, and other problems. "These are people who are already hanging onto the cliff with their fingernails," he said. "Zapping them with laser might push them over the edge."

LiGHT study design. With help from patients, LiGHT compared SLT with latanoprost eyedrops as first-line treatments for ocular hypertension and glaucoma. "In the United Kingdom, we involve patients in the design of studies and ask them about their outcomes of interest," said Prof. Garway-Heath, a LiGHT coauthor. "The advice we get from patients is very helpful."

Before conducting the LiGHT study, patients told the researchers that being drop free was important to them, he said. This helped the researchers craft a different kind of study than had been done in the past, one where the main outcomes were related to patient quality-of-life (QoL) measures and cost effectiveness; an important out-

come was achieving target pressures without the need for eyedrops.

Efficacy and safety of SLT. "This study confirmed what we knew from our clinical experience—that SLT is about as effective as one drop of latanoprost," said Dr. Tanaka. "I have offered it as a first-line treatment for a while, even before studies like LiGHT." Although the study also reaffirmed Dr. Giaconi's thinking and approach, the side effects of SLT were fewer and the benefits greater than she'd previously described for her patients.

"In the LiGHT trial, lack of compliance might account for the higher rate of progression in the medically treated patients," said Dr. Tanaka. "Based on some studies, compliance rates at best may be 50% with a once-a-day drop. If you add a second drop, compliance goes down even further."

Based on previous literature, Prof. Garway-Heath was also not surprised by the efficacy and safety of the laser. "However, I was a little disappointed that we didn't see more on the quality-of-life outcomes, which all slightly favored the laser but were not statistically significant," he said. "The larger differences were, as expected, with the ocular surface questionnaire. The main QoL outcome was chosen to allow the calculation of quality-adjusted life years, but it is a fairly blunt QoL instrument."

ZAP, LiGHT, and SALT

	Participants	Length	Outcomes	Results
ZAP	889 primary angle-closure suspects Contralateral eyes as controls	72 months	Primary angle closure disease as a composite endpoint of increased IOP, PAS, or acute angle closure	A primary outcome event occurred in: • 19 treated eyes • 36 untreated eyes No serious adverse events
LiGHT	718 participants with: • 356 in the SLT group • 362 in the eyedrops group	36 months	**Primary outcome:** HRQoL assessed by EQ-5D **Secondary outcome:** • Cost and cost-effectiveness • Disease-specific HRQoL • Clinical effectiveness • Safety	**Primary outcome:** No significant difference between the two groups **Secondary outcome:** • 97% probability of SLT as first treatment being more cost-effective than eyedrops • 74.2% in SLT group required no drops to maintain IOP at target • Eyes in SLT group were within IOP targets at more visits than eye in eyedrops group • Surgery required in 11 of eyedrops group vs. zero in SLT group
SALT	96 eyes of 85 individuals randomized to one of three groups before SLT: ketorolac 0.5%, prednisolone 1%, or saline. Drops were used 4x/day for five days, starting the day of SLT.	12 weeks	**Primary outcome:** IOP at 12 week **Secondary outcome:** • IOP at 1 and 6 weeks • Patient-reported pain • Detectable anterior chamber inflammation	**Primary outcome:** Statistically significant decrease in IOP in both steroid and NSAIDs groups compared to placebo **Secondary outcome:** No statistically significant differences between groups: • In IOP at 6 weeks • In discomfort at 1 hour and 1 week • In inflammation at 1 hour and weeks 1, 6, and 12

EQ-5D: EuroQOL-5D; **HRQoL:** Health-related quality of life.

Cost-effectiveness of drops versus laser. "Given that we were expecting more or less equivalence between the two types of treatment in effectiveness, the superiority in SLT's cost-effectiveness really stood out," said Prof. Garway-Heath. However, Dr. Tanaka would expect an even larger difference in the United States because patient co-pays and deductibles can be high. If the laser doesn't have longevity, it won't save much, said Dr. Tanaka. But if bilateral SLT lasts four years, that's the equivalent of nearly 3,000 drops of medication.

Repeat treatments. "In LiGHT, repeated treatment ended up working in a lot of people," said Dr. Friedman, adding that his past practice has been to stop if the laser didn't work the first time. "I will now likely change my algorithm and try again after six to eight weeks if it doesn't work the first time." In LiGHT, the second treatment actually lowered pressures relatively more than the first treatment, Dr. Giaconi pointed out.

Unlike its predecessor, SLT seems to be much more amenable to repeat treatment, said Dr. Katz. This study had a defined protocol of treating 360 degrees, but in the "real world," practices may vary, making it harder to know exactly how effective retreatment will be and for how long.

Study strengths and limitations. "Funded by the U.K.'s National Institute for Health Research, LiGHT was a large, well monitored, and very well implemented study—pretty definitive," said Dr. Friedman.

Dr. Tanaka pointed out one caveat. "The protocol doesn't reflect what U.S. ophthalmologists do in real life," he said. In the laser arm, patients received laser and a second laser if the first didn't work. If that was unsuccessful, patients were put on drops and received surgery if drops didn't control pressures. In the eyedrops arm, doctors immediately offered patients surgery if medical treatment failed.

"In the United States, we offer patients laser before surgery if they choose not to use eyedrops or if eyedrops fail," said Dr. Tanaka. "This has been the traditional paradigm for 20 years." The LiGHT protocol largely explains why 11 patients in the medically treated group needed surgery, he said. If they had been offered laser before surgery, this number might be lower.

Change practice? "Like many other ophthalmologists, I often didn't think of laser as part of the first-line treatment conversation," said Prof. Garway-Heath. "Now I do. It's routine for me to tell patients that they have three options—either to be observed, have laser, or have drops."

If you are a public health official, the results of the study would suggest laser for everybody with early-to-moderate open-angle glaucoma, said Dr. Katz, and the addition of medications and other surgery as needed. "But talking to an individual is different than looking at this from a public health perspective," he said, adding that he doesn't like to push patients against the wall. However, the study does help with these conversations. "I feel more confident telling patients that we have a study strongly supporting laser as a first-line therapy."

Dr. Giaconi agrees, and she uses the study results to reassure patients not only about laser's efficacy, but also its safety. "I explain that it rejuvenates the drain, like laser rejuvenates the skin." She also works in a VA glaucoma clinic, where SLT is often used as a last step before surgery. "I shared this paper with our residents and optometry service," she said, explaining that it often makes sense to refer patients for SLT, rather than prescribing drops and holding on to patients.

SALT: Improving SLT Outcomes With Anti-Inflammatories

SLT is relatively benign, said Dr. Tanaka. However, using more energy with certain patients, such as those with less pigment in the angle, can cause photophobia or discomfort in the hours or days after the laser—which can be bothersome in some people, he noted.

"Because they don't want to get the phone call, some physicians automatically put SLT patients on steroids or NSAIDs after SLT," said Dr. Tanaka. Others have been concerned that reducing the postlaser inflammatory response might lessen the efficacy of the laser, interfering in some way with its mechanism of action. "Nobody knew who was right," said Dr. Tanaka.

Results of the study. The purpose of SALT was to examine whether short-term topical steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) after SLT could improve its efficacy.

In fact, patients in this study who used steroids or NSAIDs did better at three months than those who did not. Compared with placebo, the steroid group had a 2 mm Hg IOP decrease, and the NSAID group had a more than 3 mm Hg IOP decrease. Dr. Tanaka found it striking that immediate postoperative treatment given only four times a day for four days could produce such a

large effect at 12 weeks. There was no difference in response at six weeks. A blunting of the inflammatory response might explain why, said Dr. Tanaka.

Study limitations and strengths. "SALT is the sort of study that is indicative, rather than definitive," said Prof. Garway-Heath. "It is quite small with only about 30 patients per group. And, even though it was randomized, there was quite a difference in the number of eyes treated—28 in the NSAIDS group and 37 in the steroid group."

Because it was left up to the clinician, there were also fairly large differences between the groups in the intensity of treatment given, he said. "In the NSAIDs group, only 25% had a 180-degree treatment and in the saline group, it was 45%," said Prof. Garway-Heath. "This might partly explain pressure differences."

This study also had a limited follow-up period. However, Prof. Garway-Heath said that the LiGHT study found two-month post-treatment pressures were a good indicator of future pressure control, suggesting that ophthalmologists should not automatically dismiss the 12-week results in SALT.

Time to change practice? Professor Garway-Heath and Dr. Katz aren't quite there yet. "I think this is good evidence but not sufficient to change practice," said Prof. Garway-Heath. Dr. Katz also has concerns about the size and length of the study, as well as questions about how clinicians' different laser practices—number of shots, amount of energy, or degree of treatment—might produce different outcomes.

On the other hand, Drs. Friedman, Tanaka, and Giaconi are less circumspect. "A short course of medication after SLT is not risky," said Dr. Giaconi, "and it is beneficial if it gains patients a few extra millimeters of mercury."

Dr. Friedman found the effect "a little biologically hard to believe. "But does it influence how I will behave?" he asked. "Yes. In my view, providing a steroid or NSAID is probably the better decision. Given the strong findings in favor of treatment, it is unlikely that a second study will show that treatment adversely affects the procedure."

Dr. Tanaka is also reassured. "This shows us that we can treat patients for comfort following a pretty benign procedure and not worry it will limit its effectiveness," he said. "It works hand in hand with LiGHT: Be generous in offering patients laser and afterward, feel free to give an anti-inflammatory."

1 He M et al. *Lancet.* 2019;393(10181):1609-1618.
2 Gazzard G et al. *Lancet.* 2019;393(10180):1505-1516.
3 Groth SL et al. *Ophthalmology.* 2019;126(11):1511-1516.
4 Vijaya L et al. *Br J Ophthalmol.* 2017;101(5):665-670.
5 The Glaucoma Laser Trial Research Group. *Ophthalmology.* 1990;97(11):1403-1413.
6 Jampel H et al. *JAMA Ophthalmol.* 2014;132(6):685-690.

MEET THE EXPERTS





David S. Friedman, MD, PhD, MPH Chair and director of glaucoma and medical director for clinical research at Massachusetts Eye and Ear and codirector of the Glaucoma Center of Excellence at Harvard Medical School, in Boston. *Relevant financial disclosures: None.*

David Garway-Heath, BSc, MBBS, MD, FRCOphth IGA Professor of ophthalmology for glaucoma and allied studies at the Institute of Ophthalmology, University College London, and consultant ophthalmic surgeon at Moorfields Eye Hospital in London. He is also the president of the European Glaucoma Society. *Relevant financial disclosures: Aerie: C; Alcon: S; Allergan: C; Bausch + Lomb: C; Pfizer: C,L; Santen: C,L,S.*

Jo Ann A. Giaconi, MD Health sciences professor of ophthalmology, Stein Eye Institute, David Geffen School of Medicine, University of California, Los Angeles. She is also chief of ophthalmology for the Greater Los Angeles Veterans Administration. *Relevant financial disclosures: None.*

L. Jay Katz, MD Director Emeritus Wills Eye Hospital Glaucoma Service and professor of ophthalmology at Thomas Jefferson University in Philadelphia. *Relevant financial disclosures: None.*

H. George Tanaka, MD Ophthalmologist at Vold Vision, Fayetteville, Ark. Dr. Tanaka is also former codirector of the Glaucoma Service at California Pacific Medical Center in San Francisco. *Relevant financial disclosures: None.*

See disclosure key, page 10. **For full disclosures,** view this article at aao.org/eyenet.

OCULUS Pentacam® AXL
The All-in-One Unit!

Visit the OCULUS booth #2247 at ASCRS in Boston

Optical biometry and inbuilt IOL formulas for any eye status

Use Total Corneal Refractive Power (TCRP) keratometry to account for individual total corneal astigmatism of every patient and select suitable aspheric, toric and multifocal IOL candidates more confidently. Perform swift IOL calculations using the inbuilt IOL Calculator, avoid manual transcription errors and optimize your personal constants.

Included: Barrett IOL formulas and customized formulas for post-corneal refractive patients

Toll free 888-519-5375 Follow us!
ads@oculususa.com www.pentacam.com

125 YEARS OCULUS®

Fact Sheet for the Comprehensive Eye Visit Codes: 92004 and 92014

Which two exam codes do you bill most frequently? The odds are that they would be the Eye visit codes for a new (92004) and established (92014) patient.

Keep this checklist handy. It will be a valuable reference for both billers and compliance departments.

Being audited? Auditors have been known to incorrectly apply the documentation guidelines for E/M codes to Eye visit codes, so make sure that the auditor has a copy of this checklist.

Defining the Codes

CMS published these two definitions.

92004: *Ophthalmological services: medical examination and evaluation with initiation of diagnostic and treatment program; comprehensive,* ***new patient,*** *one or more visits.*

92014: *Ophthalmological services: medical examination and evaluation, with initiation or continuation of diagnostic and treatment program; comprehensive,* ***established patient,*** *one or more visits.*

What is a comprehensive exam and evaluation? In brief, it is a general evaluation of the complete visual system. To bill for a comprehensive Eye visit code, you also must initiate or continue a diagnostic and/or treatment plan (see checklist).

Comprehensive or intermediate exam? The comprehensive Eye visit codes (92004 and 92014) require all 12 elements of the examination (see checklist), whereas you can submit the intermediate codes (92002 and 92012) if you've performed at least three, but fewer than 12, of them.

Comprehensive Eye Visit Code Checklist

Use this checklist for CPT codes 92004 and 92014.

History

☐ Chief complaint
☐ History
☐ General medical observation

Examination

Perform—and document—all 12 elements of the exam, unless patient age or trauma prevents you from doing so (in which case, document the reason).

☐ Visual acuity
☐ Gross or confrontation visual fields
☐ Extraocular motility
☐ Conjunctiva
☐ Ocular adnexa
☐ Pupil and iris
☐ Cornea
☐ Anterior chamber
☐ Lens
☐ Intraocular pressure
☐ Optic nerve discs
☐ Retina and vessels
☐ Dilation: As medically necessary. If not dilated, document why.

Initiation of Diagnostic and Treatment Program

Actions that could satisfy the codes' postexam requirements include, but are not limited to, the following:

☐ Prescription of medication, glasses, or contact lenses
☐ Arranging for special ophthalmological diagnostic or treatment services
☐ Consultations
☐ Laboratory procedures
☐ Radiology services
☐ Recommendation or decision for or scheduling or performance of a major (90-day global period) or minor (0- or 10-day global period) surgical procedure.
☐ Scheduling necessary follow-up of a medical problem
☐ Other: _____
_____
_____
_____

Get More Coding Help

The AAOE has developed an extensive range of coding products (aao.org/codingtools), and its experts are touring the country with Codequest, which is a half-day coding boot camp (aao.org/codequest). AAOE members can also use the eTalk listserv to crowdsource answers to their coding conundrums (aao.org/practice-management/listserv).

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

Acuity Pro 10

DIGITAL ACUITY SYSTEMS

Version 10 Launch !

Win/Mac Compatible

No Dongle Download

Sharper Optotypes

Up to 20/800

Patti Pic ® Pediatric Chart*

New Photo/Video Interface

New Macro Interface

32 and 64 bit Windows Versions

Support for HiDPI Monitors

Special Pricing for Upgrades

SLOAN / SNELLEN / NUMBERS / CONTRAST SENSITIVITY / HOTV

ALL ETDRS CHARTS / WHITE ON BLACK OPTION

SINGLE LETTER - SINGLE LINE - MULTI-LINE / 56 KEY CUSTOM REMOTE

MARCO INTEGRATION / INFINITE OR LIMITED RANDOMIZATION OPTIONS

ALL IN ONE SYSTEMS OR SOFTWARE ONLY / FREE SUPPORT/ NO ANNUAL FEES

DIASTER PROOF BY DESIGN 580.243.1301 / ACUITYPRO.COM

USED ON BOARD THE INTERNATIONAL SPACE STATION AND IN OVER 20 COUNTRIES ON EARTH

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

How Do You Know What You Don't Know?

Use the **BCSC® Self-Assessment Program** to quickly test your clinical knowledge and decision-making skills.

Pinpoint knowledge gaps with the only clinical education resource tied directly to *Basic and Clinical Science Course*™ content.

Quiz yourself with **2,600+ high-yield questions** and focus your study with **BCSC excerpts** and references with every question.

Subscribe today at aao.org/bcsc

This activity has been approved for *AMA PRA Category 1 Credit*™.

Protecting Sight. Empowering Lives.®

Practice Management Apps for Ophthalmology: How to Get Started

Everyone is pressed for time. Fortunately, becoming more efficient while saving money can be accomplished with the use of mobile apps, said Vinay A. Shah, MD, at Dean McGee Eye Institute in Oklahoma City. He estimates that he has saved an hour per day since incorporating apps into his routine. "Solely considering my use of airline and frequent flier apps, monitoring investments, and accessing email, I save a tremendous amount of time."

Apps in practice. Just as apps provide utility in your personal life, they can help manage your practice. The benefits are myriad, running the gamut from basic business functions to education and finding patients the least expensive medications.

Not app savvy? For those who haven't used apps, it can be reassuring to know that finding and purchasing these apps is relatively easy and inexpensive.

Getting Started

Plenty to choose from. "Anything and everything you can imagine is available as an app," said Dr. Shah. Indeed, if you don't stay focused, "it is easy to get distracted by all the extraneous information."

Where to find them. Apple's App Store remains a comprehensive resource. Access it at https://apps.apple.com/us/genre/ios/id36. Google Play also offers a wide variety of apps at https://play.google.com/store/apps.

Read the reviews. "I use Google to search for reviews of apps and try out those that appear to be a good fit," said Howard Chen MD, a solo practitioner in Goodyear, Arizona.

Typically, apps come at little or no cost. "I spend mere pennies for most of the apps that I use, and their utility far outweighs the cost," said Ken Lord, MD, who practices in St. George, Utah.

How many apps on your phone? Not so long ago, phones had limited storage, and underutilized apps had to be deleted to make space for other tasks. Because cellphones now come with copious amounts of memory and everything can be backed up to the cloud, storage is not an issue, said Dr. Shah. "I regularly use 25 to 30 apps, but at one time, I counted 100+ apps on my phone," he said.

Some ergonomic rules of thumb. Your neck and fingers are susceptible to pain, stiffness, and other issues by not using proper posture and technique when accessing your apps. Dr. Shah, whose daily screen time is between three and four hours, said, "Use different fingers when typing and keep your neck up, rather than down, when looking at your device. It is much better to lift your phone than to bend your neck. Repetitive hand movements can lead to carpal tunnel–like issues [texting thumb] and other issues with your hands, as well as pain or tension in your neck [texting neck]."

BY LESLIE BURLING, CONTRIBUTING WRITER, INTERVIEWING **HOWIE CHEN, MD, KEN LORD, MD,** AND **VINAY A. SHAH, MD.**

AAO Mobile App

The Academy's AAO Ophthalmic Education App features content from EyeWiki and three areas of the ONE Network: News, 1-Minute Videos, Diagnose This, and, coming later this year, *Wills Eye Manual.* Customize your feed based on your area(s) of interest to view content and receive alerts when relevant content is published.

For more information, go to aao.org/education-app.

Apps to Consider

Centralize communications. Google offers G Suite, which can serve as a "backbone for your business' infrastructure," according to Dr. Lord. Collaborating via secured messaging, attending video conferences, emailing, and sharing files are some of its most useful features, he said. "It is a really convenient way to communicate from anywhere. When exchanging patient information, we remain HIPAA compliant by using medical record numbers instead of names and birthdays," he explained. After your practice signs up for G Suite (https://gsuite.google.com), you will be charged a monthly fee depending on which edition you use and how many staff will be using it.

Online storage. The Google Drive app is a cloud-based online storage service that earns high marks from Dr. Shah. "My whole life is on Google.

Apps Developed By Your Colleagues

Save time in the clinic. EyeHandbook, developed by Drs. Shah and Lord, places multiple ophthalmic testing tools, coding guidelines, informational videos, and calculators (and much more) at your fingertips.

Educate your patients. The goal of Eye Patient, said Dr. Lord, "is to save physicians time in the lane by giving patients a solid go-to resource." In addition to providing educational videos, this app allows patients to monitor their vision with functions like the Amsler grid, and it can assist them in their daily life with a magnifier function, he said.

I can organize my documents and share them with friends, family, staff, and colleagues," he said.

Track expenditures. Keeping up with costs is easy with Expensify and QuickBooks. "My favorite app is Expensify because it enables me to do the bookkeeping for my practice, which, with the app, takes me less than 30 minutes per month and eliminates my need for an accountant. I am able to upload my receipts to the cloud and can create monthly reports, as well as create reports for my equipment, food, and mileage, for example," said Dr. Chen.

QuickBooks has similar functionality, plus a payroll option, he said.

Check your credit score. Keeping tabs on your credit score may be particularly significant to ophthalmologists who have outstanding student loans or those who are looking to open a practice. Dr. Chen recommended using either the Credit Karma or Experian apps.

Process credit card payments. There are multiple credit card processing services. Dr. Chan has had a good experience with the SwipeSimple app, which is available through Payment Depot (http://paymentdepot.com/l-swipesimple/). He advises looking for transparency in fees, and he warned, "Do not get locked into a contract with early termination penalties. Many companies promise to beat their competitors, but customers frequently discover that their fees are much higher after receiving the first few statements."

Input contact information from business cards. With CamCard, users can take a photo of a business card, and the app will save the information to your phone's contact list, as well as import the original image. "This is a huge timesaver considering all of the business cards that physicians exchange daily," Dr. Shah said. Other options include Abbyy, ScanBizCards, Wantedly People, and Evernote.

Keep drug costs in check. Prescriptions can vary tremendously in price, depending on where they are purchased. GoodRx facilitates a quick comparison between pharmacies so patients know their most cost-effective options. Simply enter a drug name and zip code, and GoodRx lists the out-of-pocket charges at local pharmacies. "We used to ask patients to call around for the best price. Using this app not only saves time, it can potentially save your patients a lot of money," said Dr. Shah.

Dr. Chen is a comprehensive ophthalmologist and solo practitioner at Goodyear Eye Specialists in Goodyear, Ariz. *Relevant financial disclosures: Solo Building Blogs: O.*

Dr. Lord is a retina specialist at Retina Associates of Southern Utah in St. George. *Relevant financial disclosures: EyePatient: O.*

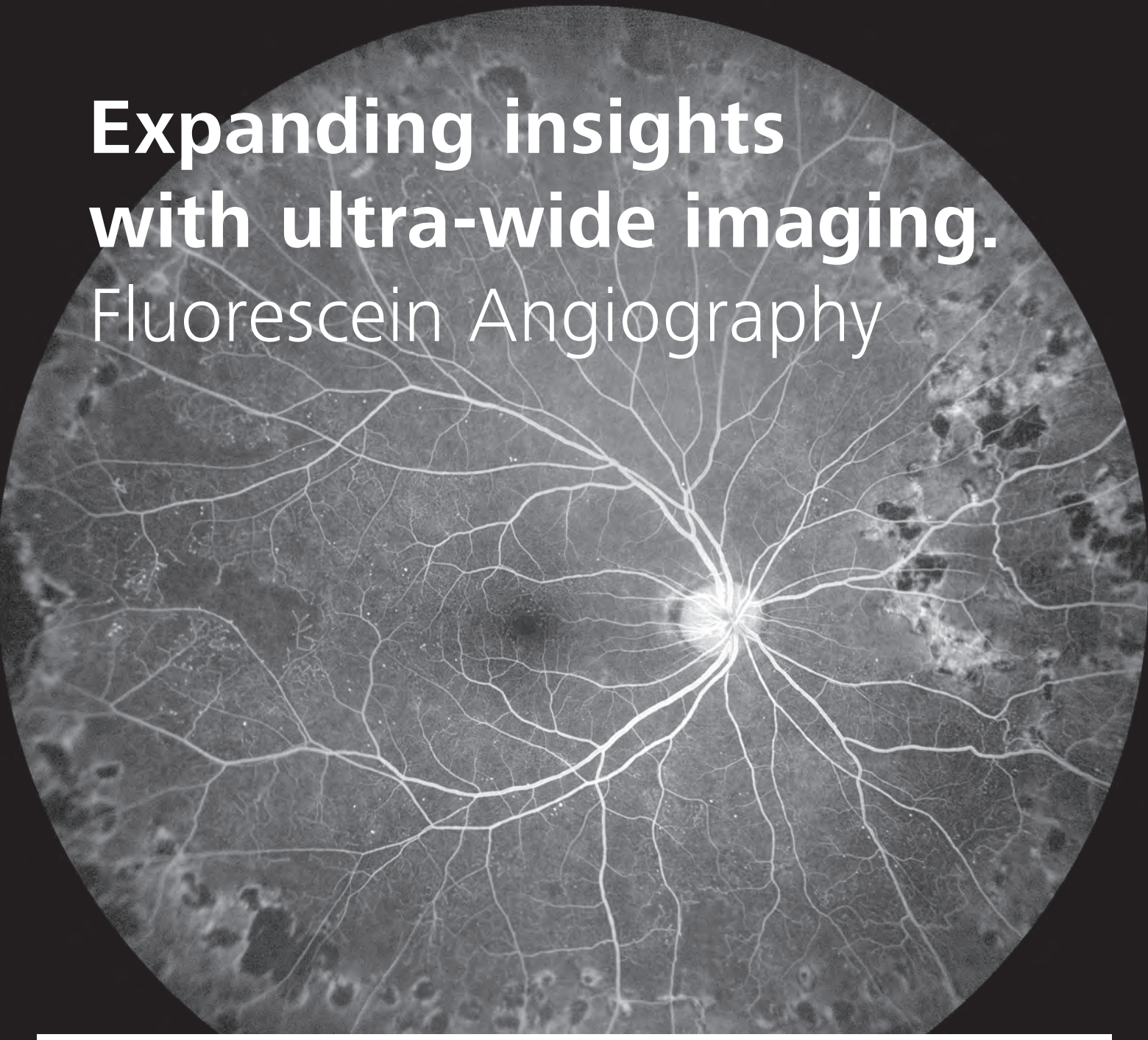
Dr. Shah is a vitreoretinal specialist at the Dean A. McGee Eye Institute and clinical professor of ophthalmology at the University of Oklahoma, Oklahoma City. *Relevant financial disclosures: Cloud Nine Development: O. Eye Patient: O.*

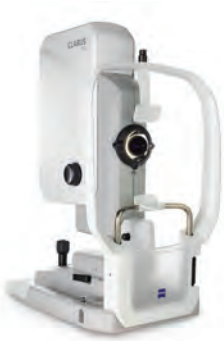
See disclosure key, page 10. **For full disclosures,** see this article at aao.org/eyenet.

EXTRA **MORE ONLINE.** For tips on monitoring personal finances, see this article at aao.org/eyenet. Got a favorite app? Use the article's comments section to recommend it to your colleagues.

Expanding insights with ultra-wide imaging.

Fluorescein Angiography





ZEISS CLARUS 700

Color. Clarity. Complete.

CLARUS® 700 from ZEISS offers fundus fluorescein angiography (FFA) in an ultra-widefield view. Its high-resolution images provide detailed visualization of the retina—helping to identify capillary non-profusion and intraretinal microvascular abnormalities—which is important in cases such as diabetic retinopathy where subtle details can inform the diagnosis.

www.zeiss.com/us/clarus700

ZEISS

Seeing beyond

CAM.11533 Rev B Contact a local representative for regulatory status and approved labeling.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

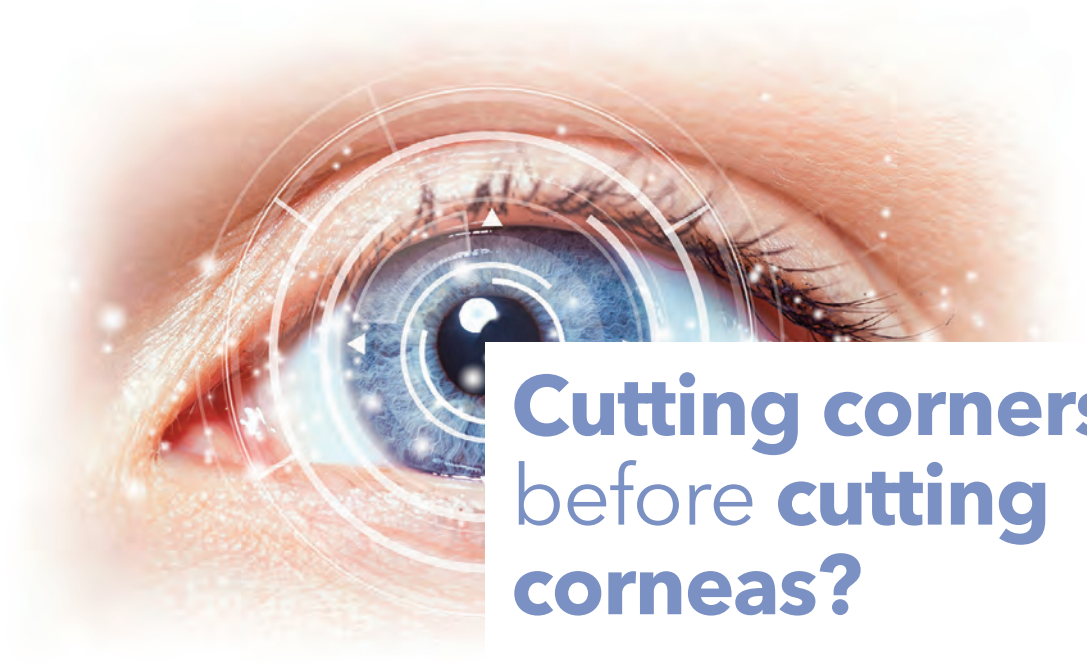
Empower Your Entire Practice Team

Join the American Academy of Ophthalmic Executives® (AAOE®)

AAOE, the Academy's practice management affiliate, offers the expert support you and your team need to run a successful modern practice.

- **Free online coding and practice management courses**
- **Strategic business intelligence**
- **AcadeMetrics™ benchmarking and financial tools**
- **Generous member pricing for Academy products and expert consultations**

See how AAOE membership works for you at **aao.org/aaoe**



Cutting corners before cutting corneas?

If you haven't been testing for MMP-9 you might be.

If elevated MMP-9, a key inflammatory biomarker for dry eye, is tested for and detected prior to surgery, you have an opportunity to customize your treatment plan which may improve post-surgical outcomes and reduce complications.

InflammaDry, the one-and-only rapid point-of-care test that detects MMP-9

- CLIA waived
- Results in minutes
- 4 simple steps
- Minimally invasive
- Requires no special equipment

Stop cutting corners and start testing with InflammaDry today. Contact your Quidel Account Manager at **800.874.1517**.

QUIDEL | InflammaDry®

quideleyehealth.com

AD10241500ENO00 (08/19)

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

AAO 2020 VISION

Registration Opens in April for AAO 2020 in Las Vegas

April 8 (Academy and AAOE® members)
April 22 (Nonmembers)

AAO 2020 November 14 – 17
Subspecialty Day November 13 – 14
AAOE® Program November 13 – 17
ASORN Nursing Program November 13 – 14

Hear From Michael X. Repka, MD, 2020 Jackson Memorial Lecturer

Michael X. Repka, MD, will deliver the 77th Edward Jackson Memorial Lecture — the most distinguished lecture in ophthalmology. He'll address the future of amblyopia with "Improving Amblyopia Outcomes Through Clinical Trials and Practice Measurement."

Feel the Energy of Las Vegas

While you're in town, see the world's top performers in any one of dozens of shows. Book your tickets ahead of time to see the likes of Blue Man Group, Cirque du Soleil, Motown Extreme, La Rêve, David Copperfield, and more.

Where All of Ophthalmology Meets®

aao.org/2020

Protecting Sight. Empowering Lives.®

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

AAO 2020 Opening Session: Don't Miss These Lectures

Mark the Opening Session on your calendar. Highlights will include talks by Malcolm Gladwell and Michael X. Repka, MD. The AAO 2020 Opening Session starts at 8:30 a.m. on Sunday, Nov. 15, in Las Vegas.

Malcolm Gladwell will give the keynote speech. He is an internationally known journalist, writer, and cultural observer. He has been included in the *Time* 100 Most Influential People list and has appeared in *Foreign Policy* magazine's list of Top Global Thinkers. His work, which focuses on human psychology and sociology, appears in *The New Yorker* where he has been a staff writer since 1996. He is also the author of six *New York Times* bestsellers: *The Tipping Point, Blink, Outliers, What the Dog Saw, David and Goliath,* and his recently published book, *Talking to Strangers.*

Mr. Gladwell is also the cofounder of Pushkin Industries, an audio content company that produces podcasts, such as Solvable, Against the Rules, and The Happiness Lab. He also hosts Revisionist History, which "reconsiders things both overlooked and misunderstood," and cohosts Broken Record, where he interviews musicians.

OPENING SESSION. *Mr. Gladwell's keynote will be one of many highlights at AAO 2020. For information on the Subspecialty Day program, course passes, and ticketing, see page 64.*

Michael X. Repka, MD, will present the Jackson Memorial Lecture. His talk is titled "Improving Amblyopia Outcomes Through Clinical Trials and Practice Measurement."

Dr. Repka is internationally recognized for his contributions in the fields of pediatric ophthalmology, strabismus, retinopathy of prematurity, and pediatric neuro-ophthalmology. His clinical practice includes an interest in the management of strabismus and amblyopia.

Dr. Repka is the David L. Guyton, MD, and Feduniak Family Professor of Ophthalmology at Johns Hopkins University's Wilmer Eye Institute in Baltimore. He is also the Academy's medical director for Governmental Affairs and the ophthalmology advisor on the American Medical Association's CPT Advisory Committee.

Register for AAO 2020 and Book Your Hotel

Starting April 8, Academy and American Academy of Ophthalmic Executives members can register and make hotel reservations for Subspecialty Day (Nov. 13-14), AAO 2020 (Nov. 14-17), and half-day AAOE Coding Sessions (Nov. 14) in Las Vegas. Nonmembers can do so starting April 22. Find more information at aao.org/registration and aao.org/hotels.

Remember: Registration for AAO 2020 is free if you are a member and your 2020 membership dues have been paid. Join or renew today at aao.org/member-services.

Avoid scams: Book hotel rooms and register only through links provided by the Academy. Several fraudulent companies pretending to be associated with the Academy and AAO 2020 may appear in web searches or may have already contacted you via email. They claim that they can book hotel rooms or register you for the Academy's annual meeting, but they are unaffiliated with the Academy. The official hotel reservation provider for AAO 2020 is Expovision.

If you are ever in doubt, email meetings@aao.org, call 1-415-561-8500, or contact Expovision at aaohotels@expovision.com or toll-free at 1-866-774-0487.

Mid-Year Forum N

CANCELED

This year's Mid-Ye (MYF) takes place A and puts the focus o olitics, and practice ma t. Hear the keynote speech

AMERICAN ACADEMY OF OPHTHALMOLOGY®

by U.S. Surgeon General Jerome M. Adams, MD, MPH, meet your legislators during Congressional Advocacy Day (see Volunteer Opportunity below), attend the Academy Council meetings (April 24 and 25), pick [illegible] range of discussion sessions [illegible] more. For the full schedul[illegible].org/myf.

Not [illegible]ed yet? The deadline for advan[illegible]gistration is April 6, but you can also register onsite. Learn more at aao.org/mid-year-forum/registration-travel.

Get the latest news. Reports from the Mid-Year Forum will be posted at aao.org/mid-year-forum/news.

TAKE NOTICE

MIPS—Are You on Schedule With Your 2020 Reporting?

There are several ways to report MIPS quality measures this year, but no matter which option(s) you choose, you should have already made a start on reporting quality.

Reporting via Medicare Part B claims. Reporting via claims needs to be done in real time. If you plan to meet the 70% data completeness criteria, you probably should have already started reporting quality measures.

Reporting manually via the IRIS Registry. Have you already entered your quality measure data from January, February, and March into the IRIS Registry? If not, you should start catching up. Although manual reporting via the IRIS Registry doesn't have to be done in real time, reporting throughout the year—even each day, on a patient-by-patient basis—will make the process much more manageable.

Reporting via IRIS Registry–EHR integration. Although the IRIS Registry uses an automated process to extract quality measure data from your electronic health record (EHR) system, it is still your responsibility to check your measures at least quarterly to look for potential problems. For example, are the correct patients being pulled for a measure? Are staff entering data into the correct field of the EHR? If there are issues with your data mapping or workflow, they need to be identified and addressed as soon as possible.

Start reviewing improvement activities. New this year: Groups only get credit for an improvement activity if at least 50% of the clinicians meet the reporting requirements of that activity.

Start reviewing the promoting interoperability measures. Make sure you understand the measure requirements.

For detailed descriptions of those measures, plus the Academy guide to understanding their specifications, visit aao.org/medicare/promoting-interoperability/measures.

Who in your practice is taking the lead on MIPS? Given the amount of money at stake, you need to make sure that your practice has at least one staff point person and has named a physician as its MIPS champion.

Is your staff point person signed up with the AAOE? The AAOE is the practice management arm of the Academy. AAOE members enjoy access to all the Academy's MIPS resources (see below) and, just as importantly, they are part of an active community that frequently uses its listserv to share MIPS tips.

Use the Academy's resources:

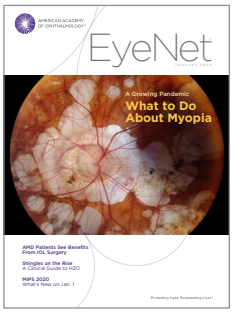
- The MIPS hub page at aao.org/medicare, which includes the "Small Practice Roadmap" and "Large Practice Roadmap."
- The IRIS Registry User Guide at aao.org/iris-registry/user-guide/getting-started.
- *EyeNet*'s *MIPS 2020: A Primer and Reference,* which has been posted online ahead of print at aao.org/eyenet/mips-manual-2020. (When the print edition arrives, make sure to give it to your MIPS point person.)

Check your email each week. Get the latest MIPS news in Washington Report Express (Thursdays) and, for AAOE members, Practice Management Express (Sundays).

If you haven't started yet, begin soon. You can sign up for the IRIS Registry at aao.org/iris-registry/sign-up. If you are already signed up with the IRIS Registry, make sure your practice and provider information is up to date.

A Request From *EyeNet*

You may have received an email invitation to participate in a magazine readership survey conducted by Kantar Media. If you are a fan of *EyeNet*, please participate and make your opinion known. Being ranked among the most widely and thoroughly read ophthalmic publications enables *EyeNet* to secure funding for projects that help you in the clinical realm and in your practice, like the MIPS manual (aao.org/eyenet/mips-manual-2020).



Volunteer Opportunity: Become a Congressional Advocate

Participate in the Academy's Congressional Advocacy Program and help drive a pro-ophthalmology legislative and regulatory agenda.

Become an effective physician advocate. With assistance from the Academy, you'll develop relationships with lawmakers to provide important constituent input and represent the Academy's key priorities. As a Congressional Advocate, you will communicate with members of Congress and congressional staff through email as well as face-to-face meetings in both Washington and their congressional district. Join this national network of ophthalmologists, which has the power to influence legislation.

Start this month at Congressional Advocacy Day (CAD). Th[illegible]ademy's Mid-Year Forum (A[illegible]kicks off with a dinner h[illegible] to prepare at[illegible] 23 appoint[illegible] of Congress. Adva[illegible]or the Mid-Year Forum[illegible]myf) closes on April 6, but yo[illegible]also will be able to register onsite.

Check aao.org/cad for the virtual advocacy day.

More on volunteering. Learn about dozens of Academy volunteering opportunities aao.org/volunteering.

Year of the Eye: Watch for the *Ophthalmology* Special Supplement

In celebration of the year 2020, *Ophthalmology* has published a commemorative supplement that will arrive in the

mail with your April issue of the blue journal. Titled *2020 Retrospective of Landmark Contributions,* the supplemental publication includes 12 studies published over the history of the journal that have had a major impact on the field, including "Prevalence of Age-Related Maculopathy: The Beaver Dam Eye Study" by Klein et al., "Herpetic Eye Disease Study: A Controlled Trial of Topical Corticosteroids for Herpes Simplex Stromal Keratitis" by Wilhelmus et al., and others. These articles were selected by the *Ophthalmology* editorial board. Companion commentaries accompany each article; these are written by well-known experts in the field, including **Emily Y. Chew, MD, Joan W. Miller, MD,** and others. The supplement is available online at aaojournal.org.

Advice From OMIC: Protect Against Giant Cell Arteritis Claims

A review of OMIC records shows that malpractice lawsuits for delay in diagnosis of giant cell arteritis (GCA) often involve ophthalmologists who had successfully treated patients with GCA in the past, knew its signs and symptoms well, and understood that emergent treatment is needed to prevent imminent, bilateral vision loss. What, then, led these ophthalmologists astray?

The OMIC article "Giant Cell Arteritis Claims Are Costly and Difficult to Defend" can be found in the 2015 *OMIC Digest* at omic.com/news-2/publications. It explores the reasons for these poor outcomes, the standard to which medical experts hold physicians who treat these patients, and the measures ophthalmologists can take to improve the likelihood of a correct and timely diagnosis. It also points to a downloadable checklist at omic.com/giant-cell-arteritis-checklist. *OMIC offers professional liability insurance exclusively to Academy members, their employees, and their practices.*

D.C. REPORT

Academy Members Call for Action on Prior Authorization

Earlier this year, Academy members from across the United States took part in the Regulatory Relief Coalition's national "day of action" to press Congress to end prior authorization abuses by Medicare Advantage plans. More than 200 Academy members sent messages to their elected officials to urge support for the bipartisan Improving Seniors' Timely Access to Care Act.

This bill aims to increase transparency and reduce costly burdens in Medicare Advantage's prior authorization process. It would:

- streamline the electronic prior authorization process;
- minimize the use of prior authorization for routinely approved services;
- ensure prior authorization requests are reviewed by qualified medical personnel;
- require transparency from Medicare Advantage plans on the extent of their use of prior authorization and rates of delay and denial; and
- prohibit additional prior authorization requirements for medically necessary services performed during preapproved surgeries or other invasive procedures.

The bill is sponsored by Reps. Suzan DelBene, D-Wash., Mike Kelly, R- Pa., Ami Bera, D-Calif., and Roger Marshall, R-Kan. Since its introduction, more than 160 lawmakers in the U.S. House of Representatives have signed on in support as cosponsors.

For the latest Advocacy news, visit aao.org/advocacy.

ACADEMY RESOURCES

New: International Retina Journal Club Webinars

A new retina journal club is starting up at the Academy. These webinar-based discussions of important retina papers will take place quarterly.

The inaugural webinar, developed in conjunction with the Sociedad Panamericana de Retina y Vitreo, will take place April 29 at 8 p.m., U.S. Eastern Time, and is titled Treatment-Naïve, Non-Exudative Macular Neovascularization in AMD. Moderators Drs. Christopher Henry and Lihteh Wu will discuss three papers with authors Drs. Luiz Roisman, Joao Rafael De Oliveira Dias Sr., and Philip J. Rosenfeld.

Participation is free of charge.

Register at aao.adobeconnect.com/rjc04292020/event/event_info.html.

Benchmark Your Practice

Academy and AAOE members can access two key benchmarking tools and garner valuable analytics that have helped practices increase revenue, justify new staff hires, and more.

Benchmarking Survey. The Academy/AAOE AcadeMetrics practice management benchmarking survey opens April 15 and closes July 31, so act quickly to benefit from this valuable tool. Enter your 2019 practice management data by the deadline and use the AcadeMetrics benchmarking tool throughout the year to compare your financial data to that of similar practices. Get valuable insight into optimal staffing levels, number of satellite offices, and more.

Ophthalmic Salary Survey. Another AcadeMetrics tool—the Ophthalmic Salary Survey—is open year-round and tracks specific benchmarks related to optometrist, midlevel provider, and staff salary data to help you benchmark compensation and benefits packages.

Get started at aao.org/academetrics.

Access Trusted Business Expertise

The Ophthalmic Advisors Group—composed of the Academy's senior coding and practice management experts—offers a comprehensive suite of

consultation services to help solve your practice's complex business challenges. They'll set you up for success with chart audits, coding, claims, reimbursement, business management, and staff development. Available to Academy and AAOE members through the Academy Store.

Learn more at aao.org/consultation-services.

OPAL Helps Practice Managers Become More Effective Leaders

AAOE's Ophthalmic Practice Administrators Leadership (OPAL) Program is designed especially for practice managers to move to the next level of professional growth. Program participants work one-on-one with a mentor, develop a unique capstone project, and showcase their leadership skills at a special event during the Academy's annual meeting. Applications for Cohort 2020-21 are due April 30.

For more information about OPAL, visit aao.org/practice-management/leadership-program or email aaoe@aao.org.

MEETING MATTERS

Course Pass and Tickets: Buy Them Early

Registration for AAO 2020 gives you access to sessions, papers, Poster Theater presentations and Poster Discussions, e-posters, videos on demand, coffee and conversation at the Academy Cafés, and more. For even greater access, consider purchasing the Academy Plus course pass.

Academy Plus. Academy Plus is a course pass that offers unlimited access to all Academy and AAOE instruction courses, including Skills Transfer didactic lectures. No need to plan or preselect courses. Pass holders can float among all available courses.

You can purchase the Academy Plus course pass after you have registered for AAO 2020 online. Academy Plus will also give you access to the Meetings on Demand, which highlights presentations recorded during the annual meeting.

Ticketed events. Tickets for Skills Transfer labs, special meetings, and AAOE Practice Management Master Classes will be available for purchase starting June 17.

Visit aao.org/registration for more information.

GET READY FOR VEGAS. *On April 8, members can register and book their hotel rooms (see page 61).*

Submit an AAO 2020 Abstract Online by April 14

Contribute your expertise to the world's most comprehensive ophthalmology meeting. The online submitter for AAO 2020 paper/e-poster and video abstracts opened on March 12 and closes April 14.

The online abstract submitter for instruction courses and Skills Transfer labs closed Jan. 14.

Learn more at aao.org/presenter central.

Register for Subspecialty Day 2020

Subspecialty Day meetings feature world-renowned ophthalmologists presenting the latest developments and pearls. Dates are as follows:

- **One-day meeting on Friday, Nov. 13:** Refractive Surgery
- **Two-day meeting on Friday, Nov. 13, and Saturday, Nov. 14:** Retina
- **One-day meetings on Saturday, Nov. 14:** Cornea, Glaucoma, Ocular Oncology/Pathology, Oculofacial Plastic Surgery, Pediatric Ophthalmology, and Uveitis

Subspecialty Day registration provides attendees the flexibility to float among meetings. One-day meeting registrants can attend any of the meetings taking place that day; two-day registrants are free to attend any Subspecialty Day presentation taking place on Friday or Saturday. In addition, those registered for a Subspecialty Day meeting taking place on Saturday will have access on that day to the AAO 2020 Exhibition.

Meetings on Demand is complimentary. All Subspecialty Day meeting attendees receive access to the All-Subspecialty Day 2020 Meetings on Demand product, which captures presentations from all eight Subspecialty Day meetings.

Find more information at aao.org/subspecialty-day.

PASSAGES

Juan T. Verdaguer, MD

The influential Chilean ophthalmologist **Juan T. Verdaguer, MD,** passed away on Feb. 25, 2020, after a long illness. He was 86 years old.

Dr. Verdaguer attended medical school at the University of Chile, and at the University's JJ Aguirre Clinical Hospital, he studied ophthalmology under his father, Professor Juan Verdaguer Planas. He did postgraduate work in the United States at both Harvard and Columbia Universities.

Later he would become Professor of Ophthalmology and an Honorary Professor of the Faculty of Medicine at the University of Chile. He also served as Professor of Ophthalmology at the University of Los Andes and Academic Director of Los Andes Ophthalmological Foundation.

He was President of the Chilean Society of Ophthalmology from 1971-1972, and President of the Pan-American Association of Ophthalmology from 1997-1999. He received the 2014 National Prize for Medicine and was the Guest of Honor at the XXXIII Pan-American Congress of Ophthalmology in Lima. In addition to receiving many honors and medals, he authored more than 200 papers on retinal diseases, ophthalmic oncology, and blindness prevention.

Dr. Verdaguer is survived by his wife, Martina, four children, and 14 grandchildren, including his granddaughter, Sofia, who is a fourth-generation ophthalmologist.

MYSTERY IMAGE

BLINK

Angela Chappell, CRA, OCT-C, Flinders Medical Centre Ophthalmology Department, Adelaide, Australia.

WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments.*

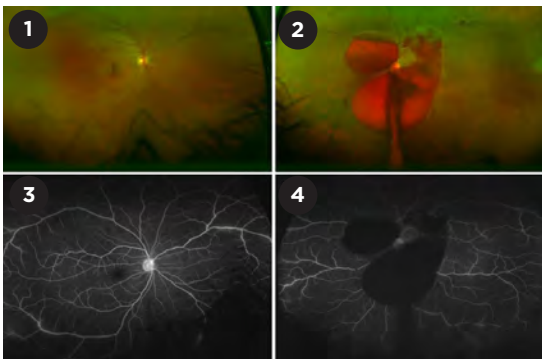
LAST MONTH'S BLINK

An Unusual Presentation of Sarcoidosis

A 29-year-old man with a history of chronic cough, pleuritic chest pain, night sweats, and multiple hospitalizations for pneumonia presented with a one-day history of sudden-onset decreased vision in his left eye. He also had a history of working in methadone clinics, and his tuberculosis status was unknown.

His visual acuity was 20/20 in the right eye and counting fingers at 3 inches in the left. Examination revealed 1+ vitreous cells and perivenous sheathing in his right eye (Fig. 1). In his left eye, 2+ vitreous cells, large preretinal vitreous hemorrhage overlying the macula and surrounding the optic nerve, intraretinal dot-and-blot hemorrhages, and perivenous sheathing in the peripheries were evident (Fig. 2). The right fluorescein angiography demonstrates hyperfluorescence of the optic nerve and late leakage of the peripheral vessels (Figs. 3, 4).

Initial workup was significant for indeterminate Quantiferon Gold testing and elevated levels of angiotensin-converting enzyme. Chest X-ray and computed tomography revealed bilateral hilar lymphadenopathy and a 5-mm nodule in the right lower lobe of the lung. Syphilis, HLA-B27, Lyme disease, and antineutrophil cytoplasmic antibody tests were negative. The patient's pulmonologist eventually performed a lung biopsy, and the findings were consistent with sarcoidosis.



Patients with ocular sarcoidosis often present with uveitis; retinopathy and vitreous hemorrhage constitute rare clinical presentations of the disease. This case illustrates the importance of considering sarcoidosis as an etiology of vitreous hemorrhage in the setting of posterior uveitis.

WRITTEN BY **RACHEL H. LEE, MD, MPH, JEROME GIOVINAZZO, MD, RICHARD M. FRANCE, MD, AND STEPHANIE LLOP, MD,** NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI. PHOTO BY MEDICAL PHOTOGRAPHY DEPARTMENT AT NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI.

LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

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

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

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

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

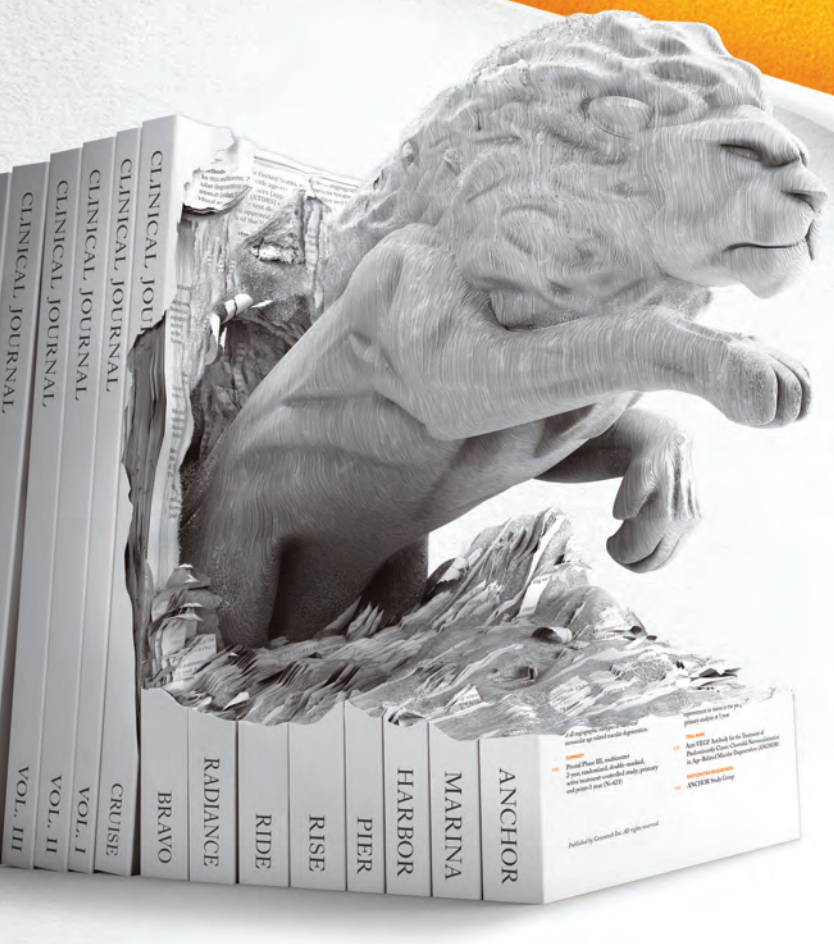
10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: M-US-00002319(v1.0) 2019

LUCENTIS®
RANIBIZUMAB INJECTION



STRENGTH IN VISION

LUCENTIS has been extensively studied and FDA approved in 5 retinal indications.

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation
- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection with LUCENTIS
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

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

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Randomized, double-masked clinical trials conducted for the 5 LUCENTIS indications included the following: **wAMD:** *MARINA, ANCHOR, PIER, HARBOR*. **DR and DME:** *RISE, RIDE*. **mCNV:** *RADIANCE*. **RVO:** *BRAVO, CRUISE*.[1-10]

REFERENCES: 1. Rosenfeld PJ, et al; MARINA Study Group. *N Engl J Med*. 2006;355:1419-1431. **2.** Brown DM, et al; ANCHOR Study Group. *Ophthalmology*. 2009;116:57-65. **3.** Busbee BG, et al; HARBOR Study Group. *Ophthalmology*. 2013;120:1046-1056. **4.** Regillo CD, et al; PIER Study Group. *Am J Ophthalmol*. 2008;145:239-248. **5.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **6.** Data on file. Genentech, Inc. South San Francisco, CA. **7.** Campochiaro PA, et al; BRAVO Investigators. *Ophthalmology*. 2010;117:1102-1112. **8.** Brown DM, et al; CRUISE Investigators. *Ophthalmology*. 2010;117:1124-1133. **9.** Nguyen QD, et al; RISE and RIDE Research Group. *Ophthalmology*. 2012;119:789-801. **10.** Ho AC, et al; HARBOR Study Group. *Ophthalmology*. 2014;121:2181-2192.

Genentech
A Member of the Roche Group