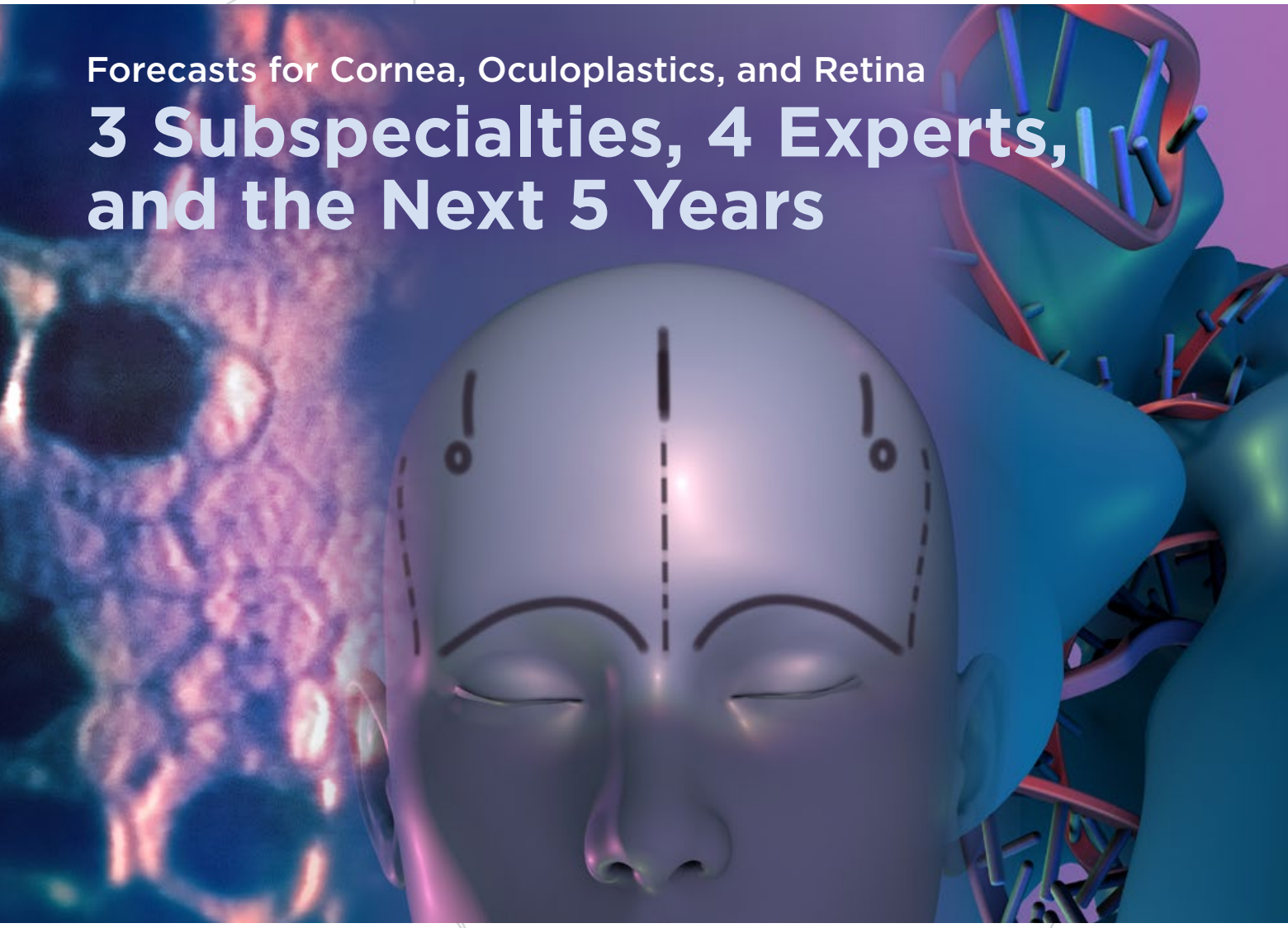
AMERICAN ACADEMY OF OPHTHALMOLOGY®

EyeNet®

DECEMBER 2017



Forecasts for Cornea, Oculoplastics, and Retina

3 Subspecialties, 4 Experts, and the Next 5 Years

CXL for Keratoconus
Watch for Intense Corneal Flattening

PEDIATRICS

Roundtable: Longitudinal OCT

Pearls: Pterygium in Young Kids

xiidra® (lifitegrast ophthalmic solution)5%

Kind of a BIIG DEAL

The first prescription eye drop FDA-approved to treat both the signs and symptoms of Dry Eye Disease

Xiidra is a lymphocyte function-associated antigen-1 (LFA-1) antagonist, the first medication in a new class of drugs.[1]

Check it out at Xiidra-ECP.com

Reference: 1. FDA approves new medication for dry eye disease. FDA News Release. July 2016. *http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm.* Accessed July 12, 2016.

Indication

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

Important Safety Information

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

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

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

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

Please see the adjacent page for Brief Summary of Safety Information and visit Xiidra-ECP.com for Full Prescribing Information.

Shire

xiidra® (lifitegrast ophthalmic solution) 5%

Rx Only

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

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

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

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

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

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

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

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

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

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

Shire

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.

For more information, go to www.Xiidra.com or call 1-800-828-2088.

US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553; 8927574; 9447077; 9353088 and pending patent applications.
Last Modified: 12/2016 S26218

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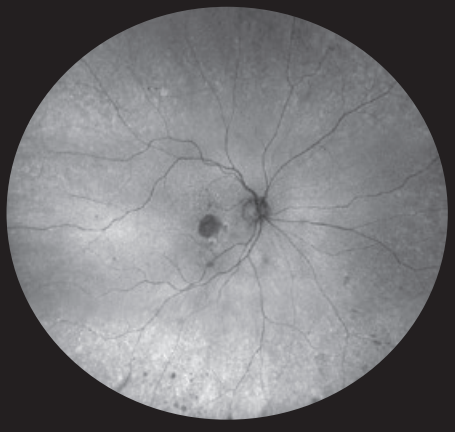

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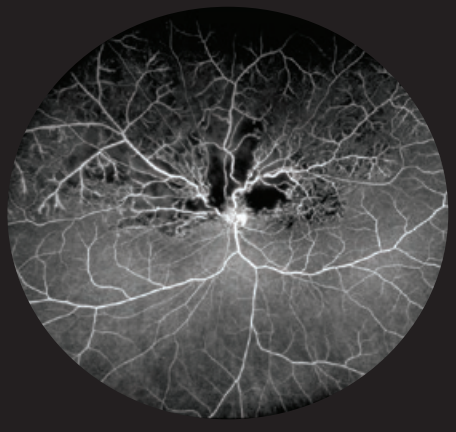

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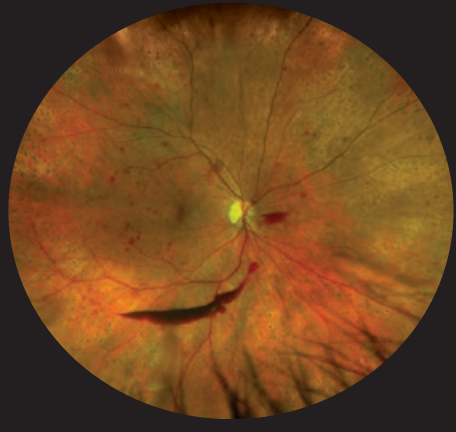

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

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

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

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 the clinical trials of another drug and may not reflect the rates observed in practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

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

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

Distributed by:

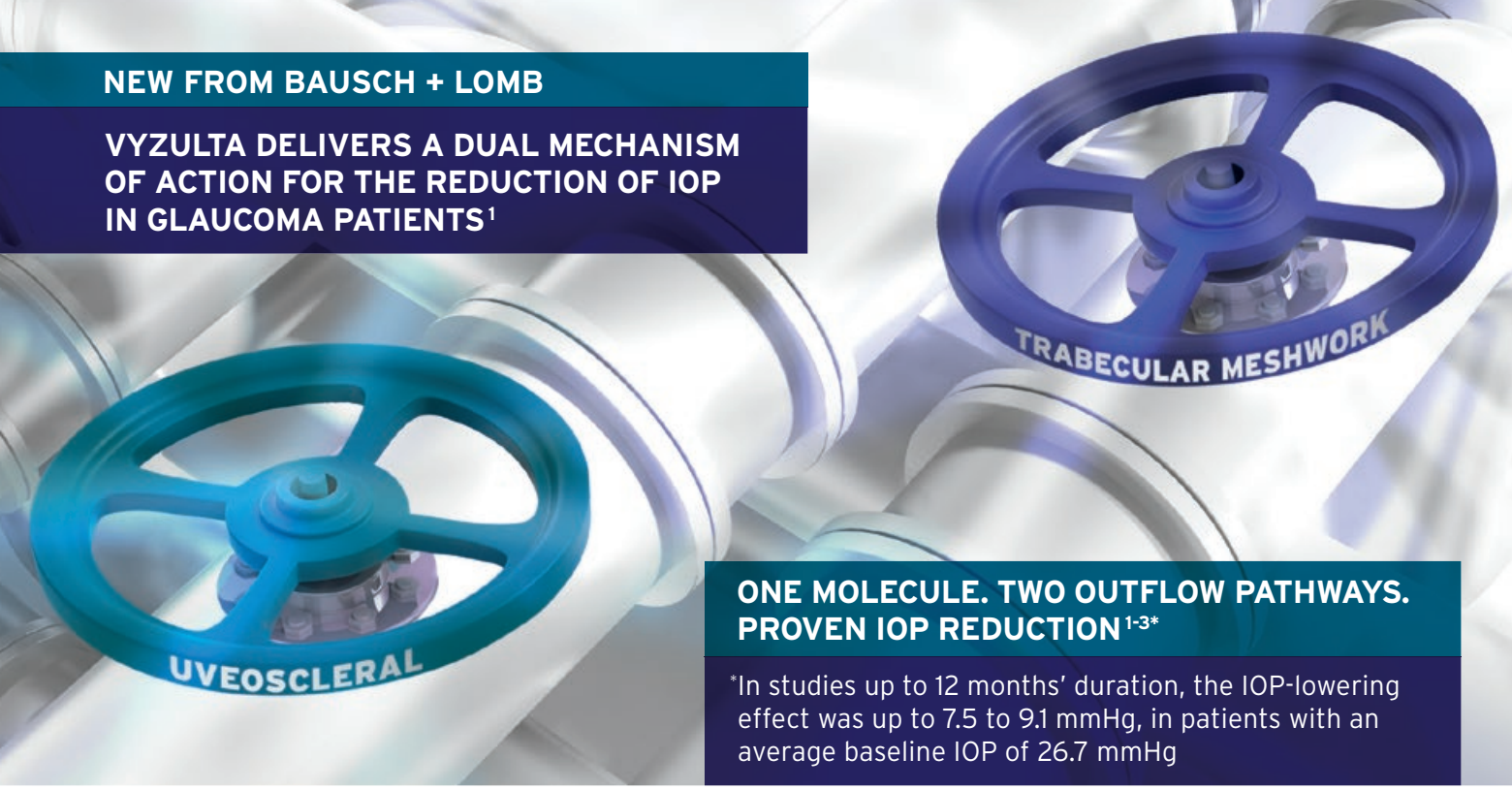
Bausch + Lomb, a division of

Valeant Pharmaceuticals North America LLC

Bridgewater, NJ 08807 USA

U.S. Patent Numbers: 6,211,233; 7,273,946; 7,629,345; 7,910,767; 8,058,467.

Based on 9464800 11/2017 VYZ.0055.USA.16 Issued: 11/2017



NEW FROM BAUSCH + LOMB

VYZULTA DELIVERS A DUAL MECHANISM OF ACTION FOR THE REDUCTION OF IOP IN GLAUCOMA PATIENTS[1]

ONE MOLECULE. TWO OUTFLOW PATHWAYS. PROVEN IOP REDUCTION[1-3*]

*In studies up to 12 months' duration, the IOP-lowering effect was up to 7.5 to 9.1 mmHg, in patients with an average baseline IOP of 26.7 mmHg

INDICATION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema

IMPORTANT SAFETY INFORMATION (CONTINUED)

- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

For more information, please see Brief Summary of Prescribing Information on next page.

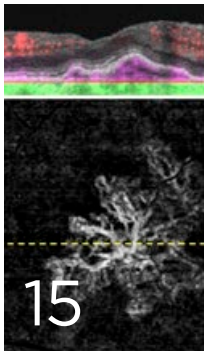
References:

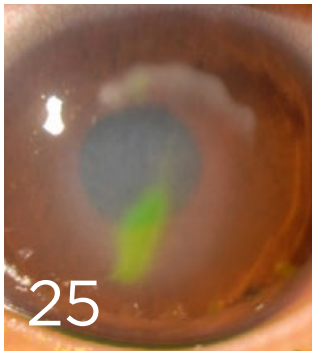
1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.
2. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
3. Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.

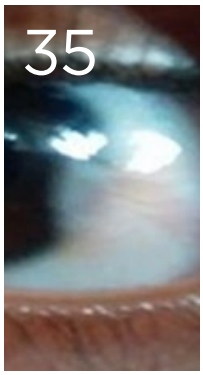
For more information about VYZULTA and how it works, visit vyzultanow.com

BAUSCH + LOMB

VYZULTA™
(latanoprostene bunod ophthalmic solution), 0.024%







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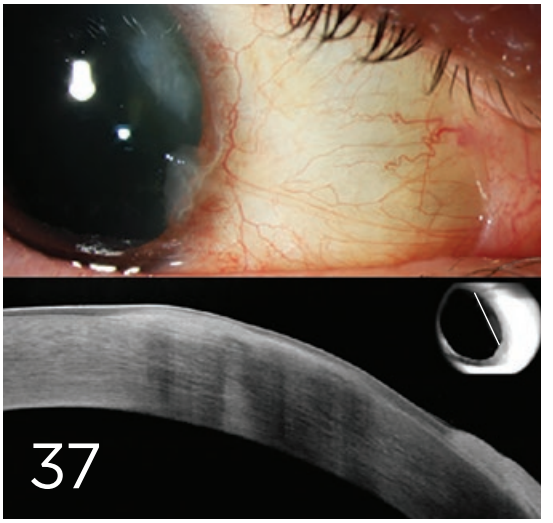
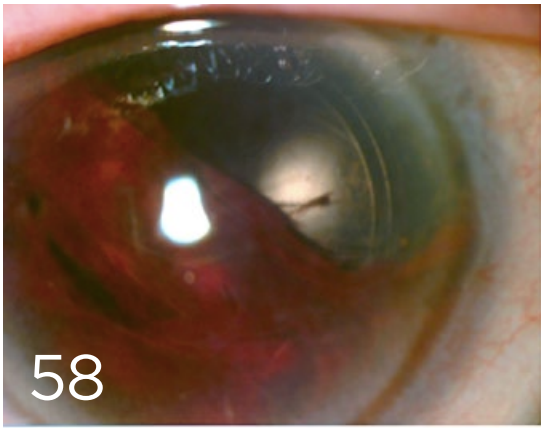
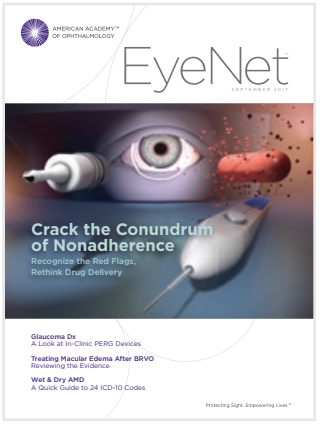




Letters



Medicare Disadvantage

I write in response to Dr. Ruth Williams' editorial "Is Medicare Advantage Driving You Crazy?" (Opinion, September). Requiring Medicare Advantage programs to provide unrestricted access to Eylea, etc., will adversely affect ophthalmology providers unless additional funds are supplied by the Centers for Medicare & Medicaid Services (CMS) to cover these inflated drug costs. With the exception of Avastin, anti-VEGF drugs are priced exorbitantly. When ophthalmologists use them in treatment protocols, medical groups and payers penalize ophthalmologists for excessively consuming the cap allowance for seniors. The Medicare Advantage insurance payers shift the costs of these medications to medical groups. These medical groups suffer financially and stigmatize/penalize the providers for these expensive treatments by cutting payments to the ophthalmology providers.

This situation is untenable without formulary restrictions requiring increased patient copays or additional money from CMS to compensate for the costs of this technology. It is no benefit to ophthalmologists to force Medicare Advantage plans to cover expensive anti-VEGF drugs, as these plans simply shift the financial risk to providers by reducing payments for professional services.

Maria Blase, Administrator
Hemet, Calif.

On Solo Practice

Dr. Williams' editorial on the state of solo practitioners (Opinion, October) garnered many online comments from your colleagues. Below is a small sample, edited and reprinted with their permission.

I have been in solo practice for 45 years and loved every minute. As Frank Sinatra said, "I did it my way." Yes, there is a price to pay in many ways, but there also is a great reward. We are fortunate in ophthalmology, like pathology, to have capable technicians help us with productivity, which makes a "solo" practice really one with many professionals. I am fortunate that my son—who also appreciates the freedom to choose when he may take a vacation or which product he must use—has now taken over the office.

I should note, however, that we have our own ambulatory surgery center (ASC) so we control everything and get both the profit and the headaches when the state shows up unannounced for an inspection. We are the only users of our ASC and run it 1 day a week. We don't make much on it, but it increases efficiency, turnaround time, patient satisfaction and convenience, and our own happiness.

Regarding electronic health records (EHRs): We have decided not to use them and to absorb the penalties for now. We feel that has increased efficiency and provided more happiness.

Frank J. Grady, MD, PhD, FACS
Lake Jackson, Texas

I started my career in ophthalmology in 1981 as a solo ophthalmologist. Over the years, I have had the pleasure of partnering with other ophthalmologists (and, on occasion, optometrists), but I will probably soon end my practice as a solo physician. I have seen a reduction of our local solo physicians in all fields of medicine. In many instances, this decline was forced by the mandatory use of EHRs. These solo physicians were either unable to afford the technology and/or unwilling to devote the time and resources to follow the government mandate. In addition, hospitals and corporate health care systems have been buying out these older solo doctors and their medical practices and replacing them with younger physicians.

In my opinion, solo physicians are like dinosaurs and will suffer the same fate of extinction. I believe that whether we like it or not, our health care system is collapsing from excessive government interference and corporate greed. I have seen virtually no evidence-based medical proof that EHRs have improved health care in the United States. In my view, EHR is really the government's control over physicians and patients, and in the United States we are evolving into a socialized form of government medicine. I am afraid that the future of health care for the American people will be a 2-tiered health care system based on wealth: those patients who can afford private insurance or fee for service, and those patients who must rely on some form of government assistance.

Charles S. Zwerling, MD, FACS
Goldsboro, N.C.

I have experienced 3 different practice models: I was in the Navy for more than 10 years, then in private group practice as an employee for 2 years, then started my own solo practice in 2009. The banks did not offer a good loan arrangement, so my husband and I maxed our 4 credit cards to open the doors, and he worked extra time at his job to pay them off. We got rid of all debt in 6 months, and the practice

started seeing steady revenue in about a year. My worst day at my own clinic (and to be honest there really aren't any bad days) is way better than my best day in the other 2 settings. Solo practices are truly more efficient and cost-effective, but of course it's not in the best interest of big organizations to admit this. You will never regret being your own boss! Having a family-run business gives you more time for your kids and more flexibility. The Merit-Based Incentive Payment System (MIPS) is a clinically irrelevant burden, but I just do the minimum so I don't sweat the penalty. If anyone wants to contact me about starting a practice, I am happy to encourage them—I have no business background, but I learned as I went. If you can go through medical school and residency and pass your boards, you can be a solo ophthalmologist.

Marjorie F. DeBenedictis, MD
Tamuning, Guam

Ho Sun Choi, MD, and I read with great interest Dr. Williams' editorial about the viability of solo practice in this era of health care consolidation. The answer to whether solo practice can survive is most definitely "Yes!"

Dr. Choi, who was mentioned in the article, started his solo practice from scratch, straight out of residency. Although it was an uphill battle, he is doing very well now. He blogged in real time about every step of practice startup. About 20 to 30 young ophthalmologists (including myself) found his blog and used it as a template to start solo practices. This is how the SoloEyeDocs Google group mentioned in the article was founded.

Drawing from our listserv discussions and Dr. Choi's original blog, we are republishing pertinent content as an updated blog: www.solobuildingblogs.com. By sharing our collective knowledge about practice startup and practice management, it is our goal to help all solo practitioners succeed.

As for the challenges to solo practice that Dr. Williams mentions in her article, here are my thoughts:

- EHR costs have been less than 2% of my gross revenues. I will have no trouble achieving a high score on MIPS.
- I found gently used equipment at favorable prices, while my former group practices insisted on paying for everything new without negotiating the price.
- If you are credentialed with the right hospital networks, IPAs, or ACOs, you can often join narrow network plans such as Medicare Advantage or exchange plans.
- Even large health systems have difficulty negotiating contracts with payers. If you can run your practice 20% more efficiently, you will come out way ahead, even with 10% less contracted reimbursement.

Our hope is that more of our colleagues, especially those fresh out of training, will read our blog and decide for themselves that solo practice is viable and perhaps even the best option for their careers. We believe that the field of ophthalmology, as well as the rest of medicine, will be stronger if more doctors are in solo practice.

Howie Chen, MD
Phoenix

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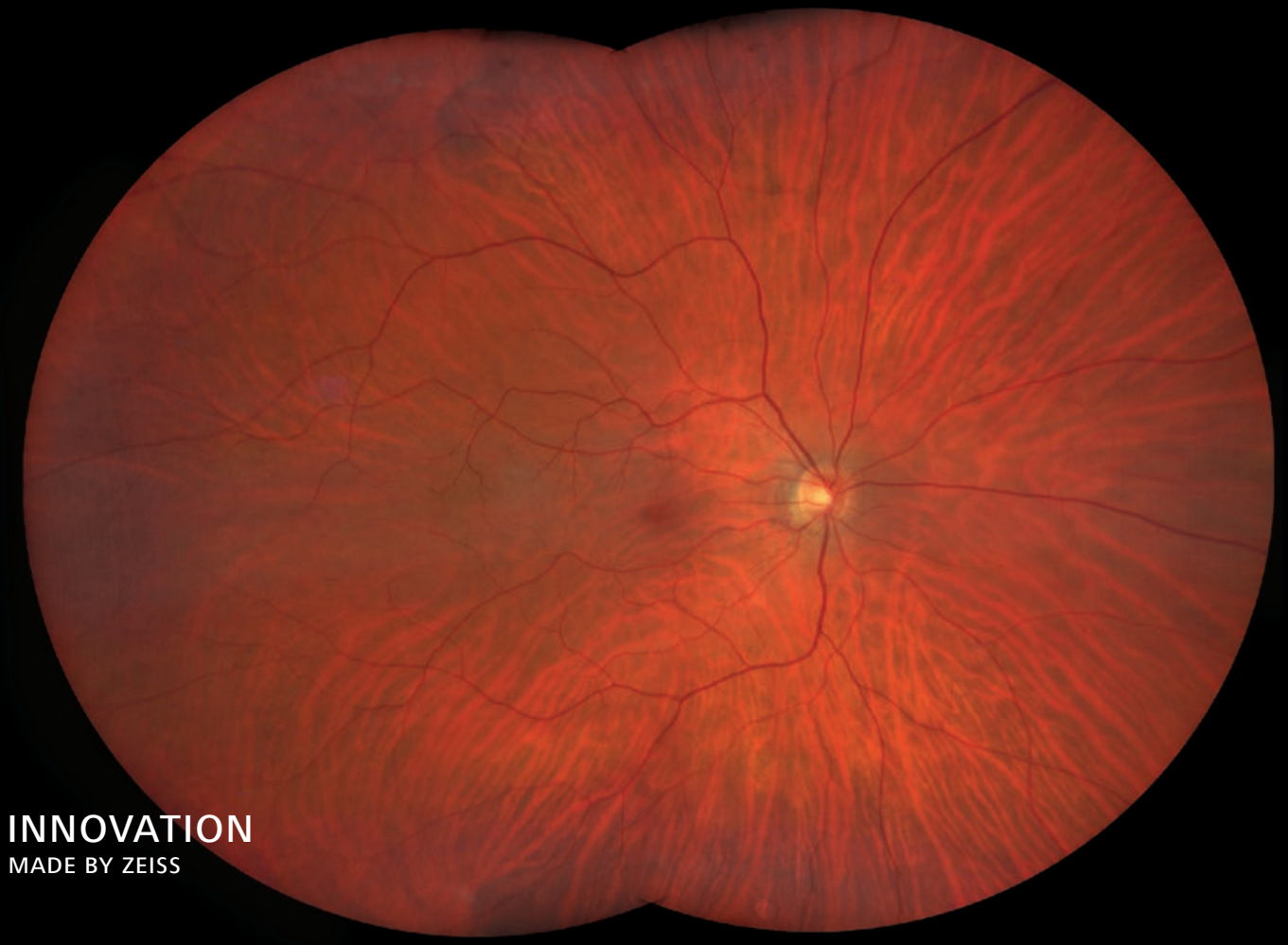

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Opinion

RUTH D. WILLIAMS, MD

Second Opinions: Value or Waste?

It's urban legend that the second opinion is the correct one. We've all given second opinions and had patients who seek them. Yet, if the first and second opinions don't align, how does the patient know which one to take?

Patients seek second opinions for a variety of reasons. One of the most common is a breakdown in communication. Patients report that the doctor didn't listen to their concerns, didn't explain the procedure, or was rushed. Sometimes patients don't want to accept the initial recommendation and are looking for alternative advice. I recently saw a patient for a third opinion who simply did not want to have glaucoma surgery despite high pressures and a deteriorating visual field. She was looking for someone to agree with her plan.

Often, the second or third physician seems better informed or a better communicator, but this characterization can be unfair. As patients process information and hear things again, they gradually accept the advice and understand the disease and its treatment. A good tactic is to ask patients why they are seeking a second opinion and then to clarify exactly what they hope to achieve during the consultation. A well-known customer service strategy is to ask, "Were all your concerns addressed?" It's common that patients feel more comfortable with the second physician because they have the chance to articulate their concerns, not necessarily because the care is better. However, some physicians are simply better communicators—and, sometimes, a different physician is a better personality fit for a patient.

While the second opinion is often an exercise in reassurance, it may well reveal a diagnostic error. Mayo Clinic researchers reviewed 286 charts of patients referred to their Internal Medicine Division and found that the original diagnosis differed significantly from the final diagnosis in 21% of cases.[1] More often, however, there are multiple treatment options for a chronic and complex disease. This is especially true during times of innovation. For example, there are many new surgical options for glaucoma treatment. One surgeon might recommend traditional filtering surgery, while another recommends a MIGS procedure combined with cataract surgery. The palette of glaucoma surgical options is dizzying for the patient—and even for the ophthalmologist. One choice isn't necessarily right or wrong, and this can be confusing for the patient. It's important to explain the rationale for the recommended treatment and to support the rationale for the original recommendation (unless it is frankly wrong). Part of educating patients is helping them understand that disease is complex and that there are nuances to treatment choices.

It's difficult to determine the value of second and third opinions. If the consultation corrects a misdiagnosis or recommends an evidence-based strategy for treatment, then it improves patient care. If the second opinion results in a less costly treatment or averts inappropriate surgery or medicine, then it is cost-effective. While second opinions might help an individual patient, we don't yet know if they lead to better health outcomes.

A number of hospitals and digital health companies offer online second opinion services. Cleveland Clinic's MyConsult online offers review and recommendations for $565-$745. Although Medicare and most insurances don't reimburse for online consultations, some employers offer the service as an employee benefit.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Second opinions—whether in person or online—will continue. Excellent medical decision-making will continue to require wise, thoughtful, experienced advice from the physician. Most of the time, this occurs face-to-face between a patient and an ophthalmologist. Occasionally, consultation with another ophthalmologist is helpful. Ophthalmologists must be open to accepting or suggesting a second opinion when our patient needs another approach or another viewpoint. Likewise, we help the patient make a good decision when we are respectful and supportive while providing the second opinion. It's still a very human process.

1 Van Such M et al. *J Eval Clin Pract.* 2017;23(4):870-874.

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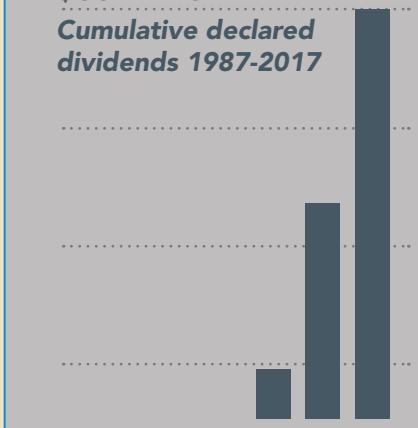

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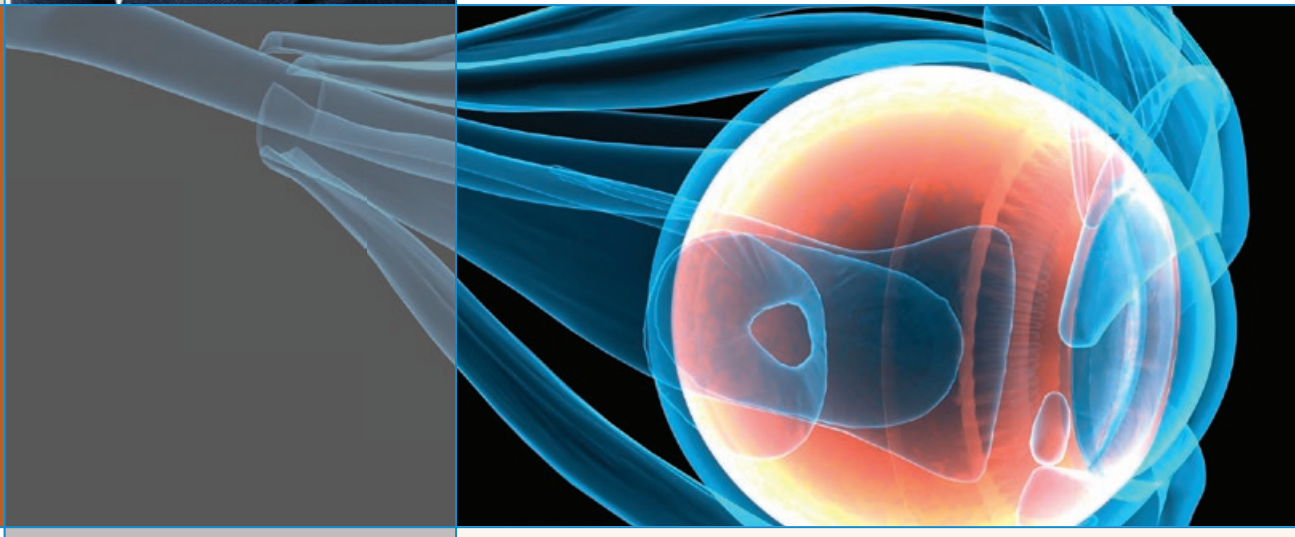

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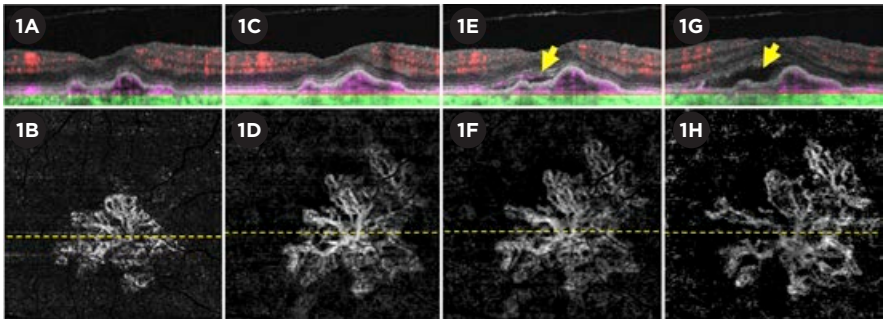

CONVERSION. *This eye had subclinical type 1 MNV at baseline (1A, 1B) and demonstrated exudative disease during 24 months (1G, 1H) of follow-up. (Top images, OCT B-scan; bottom images, SS–OCT-A. Arrow = increase in subretinal fluid.)*

RESEARCHERS HAVE KNOWN SINCE the 1970s that subclinical neovascularization could exist in eyes with dry age-related macular degeneration (AMD).[1,2] Two decades later, indocyanine green angiography (ICG) showed that, in patients with wet AMD in one eye and dry AMD in the other, these subclinical features were a strong predictor for development of exudative disease in the second eye.[3,4] However, monitoring eyes with repeated ICG testing was too invasive and expensive to be practical.

Now, results of a study using swept-source optical coherence tomography angiography (SS–OCT-A) suggest that the technique might enable ophthalmologists to not only identify eyes with these risky subclinical lesions but also quickly begin treatment when symptomatic leakage occurs.[5]

Predicting risk. For this prospective study, researchers used SS–OCT-A to monitor the disease status in 160 eyes with intermediate dry AMD or geographic atrophy (GA). The patients had wet AMD in the fellow eye.

The investigators found that, after 1 year of follow-up, exudative disease developed in 21.1% of the eyes with subclinical macular neovascularization (MNV) at baseline. The risk for exudation was 15.2 times greater (95% confidence interval, 4.2 to 55.4) compared with eyes without subclinical MNV, the scientists reported.

"This has enormous predictive value. It provides us with a tool that allows us to identify those patients who are most at risk, so they don't fall through the cracks," said coauthor Philip J. Rosenfeld, MD, PhD, at the Bascom Palmer Eye Institute in Miami.

"This finding alone—that we can identify these subclinical lesions long before exudation occurs—provides all the rationale we need to justify the use of this noninvasive, safe, and easily performed technology to survey all our patients with intermediate AMD or geographic atrophy," Dr. Rosenfeld said.

Additional findings. The researchers also reported the following results:

- Overall, 14.4% of the 160 study eyes showed subclinical MNV at baseline.
- One year after the first observation of subclinical MNV (either at baseline or during follow-up), 24% of these eyes developed exudation.
- Of the eyes without subclinical MNV on their initial angiogram, 5.4% developed it within 1 year. In these eyes, a druse-like elevation of the retinal pigment epithelium (RPE) was identified at the site. "We believe that these RPE elevations were the first sign of type 1 MNV and can serve as harbingers of impending exudation," the authors wrote.

An essential technology? Dr. Rosenfeld said he views OCT-A as "a requirement for anyone with dry AMD." If subclinical neovascularization is present, he repeats the procedure at least every 2 months. However, he initiates treatment only if the patient becomes symptomatic, he said.

OCT-A can be used to help ophthalmologists avoid unnecessary intravitreal injections, Dr. Rosenfeld said. "Treat as early as possible, but don't treat unless there's exudation. Remember that fluid can come and go in the retina of a patient with dry AMD in the absence of neovascularization, without serious consequences," he said. "And SS–OCT-A can identify those patients who have fluid in the absence of neovascularization."

Dr. Rosenfeld said the barriers to greater use of swept-source OCT to monitor patients with dry AMD are financial: Specifically, the device is double the price of earlier OCT devices.

But the technique's potential to help manage dry AMD patients is enormous, he said. "This strategy will save more vision in the long run than we've been able to accomplish" with intravitreal injections, he said. "We'll be able to treat as soon as symptomatic exudation occurs. Home monitoring will be important as well, but now we can select those patients at highest risk even when they don't have the typical high-risk fundus findings on exam."

—Linda Roach

1 Sarks SH. *Br J Ophthalmol.* 1973;57(12):951-965.
2 Green WR, Key SN III. *Trans Am Ophthalmol Soc.* 1977;75:180-254.
3 Schneider U et al. *Int Ophthalmol.* 1997;21(2):79-85.
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5 de Oliveira Dias JR et al. *Ophthalmology.* Published online Sep 27, 2017.

Relevant financial disclosures—Dr. Rosenfeld: Apellis: C,O; Carl Zeiss Meditec: C; Genentech: C,S.

CATARACT

Barrett II Formula Appears Best For 2 Popular IOLs

FOR 2 WIDELY USED INTRAOCULAR lens (IOL) models, cataract surgeons can attain the lowest levels of refractive prediction error with the Barrett Universal II formula, an analysis of 18,501 cases has found.[1]

"We found that the Barrett was the most accurate across all eyes," said Ronald B. Melles, MD, at Kaiser Permanente in Redwood City, California.

Study specifics. To conduct the study, the researchers used data from 18 months of consecutive procedures performed in the Kaiser Permanente Northern California region. In roughly two-thirds of the cases (n = 13,301), patients received an SN60WF IOL (AcrySof IQ, Alcon) in 1 eye; for the remainder (n = 5,200), an SA60AT IOL (AcrySof Natural, Alcon) was implanted (again, in 1 eye). These 2 IOLs are the most commonly used IOLs at their institution, the researchers noted.

The 145 surgeons involved used standardized preoperative and surgical protocols and a single type of biometer (Lenstar 900, Haag-Streit). They then applied 11 IOL power formulas to the preoperative measurements in each case for the purposes of calculating spherical equivalent formula predictions and comparing the accuracy of the predictions after lens constant optimization.

GLAUCOMA

Eye on Glymphatic System

A TEAM OF GLAUCOMA RESEARCHERS HAS PRO-posed that a paravascular transport system exists in the eye and optic nerve—and that this pathway is likely continuous to a paravascular pathway in the brain known as the glymphatic system.[1]

Brain researchers have proposed that a disturbance of flow of cerebrospinal fluid (CSF) through paravascular pathways may contribute to the development of Alzheimer disease. Now Peter Wostyn, MD, and his colleagues suggest that a paravascular disruption between the eye and optic nerve may explain the pathogenesis of primary open-angle glaucoma (POAG). Their "glymphatic hypothesis of glaucoma" builds on research that acknowledges the collective contribution of vascular, biomechanical, and biochemical factors in the pathophysiology of POAG.

Building the hypothesis. The recently discovered glymphatic system is described as a network of paravascular pathways, or channels surrounding blood vessels, throughout the brain.[2] As CSF circulates through the brain along these pathways, it clears away waste, including amyloid-ß, a hallmark protein in Alzheimer disease. The glymphatic system also distributes other compounds, such as glucose, lipids, growth factors, and amino acids.

"The 'glymphatic hypothesis of glaucoma' suggests that glaucoma might be the result of an imbalance between production and clearance of neurotoxins in the optic nerve due to a dysfunctional ocular glymphatic system," said Dr. Wostyn, at PC Sint-Amandus in Beernem, Belgium.

"Our group has proposed that glaucoma may share a common glymphatic background with Alzheimer disease—and that glaucoma, just like Alzheimer disease, may occur when there is an imbalance between production and clearance of neurotoxins such as amyloid-ß," Dr. Wostyn said.

Finding the pathway. In a postmortem study examining cross-sections of the human optic nerve, Dr. Wostyn's group provided the first histological evidence for a paravascular pathway in the eye.[3] Subsequently, others found evidence for CSF entry into the optic nerve via a glymphatic pathway.[4]

But further evidence is needed to support the existence of a glymphatic system in the optic nerve, Dr. Wostyn acknowledged. He added that, if the presence of this system is confirmed, "emerging imaging technologies may be used to reveal ocular glymphatic abnormalities associated with glaucoma."

—Miriam Karmel

1 Wostyn P et al. *Biomed Res Int.* 2017:5123148.
2 Iliff J et al. *J Clin Invest.* 2013;123(3):1299-1309.
3 Wostyn P et al. *Clin Exp Ophthalmol.* 2017;45(5):539-547.
4 Mathieu E. *Invest Ophthalmol Vis Sci.* 2017; 58(11):4784-4791.

Relevant financial disclosures—Dr. Wostyn: None.

Prediction errors. The analyses revealed that, between axial lengths of 23 to 25 mm, most of the formulas yielded results within 0.1 D of predicted spherical equivalent. However, as axial length, keratometry, anterior chamber depth, and lens thickness varied, most formulas had "notable biases" in their prediction errors, the authors reported. For instance:

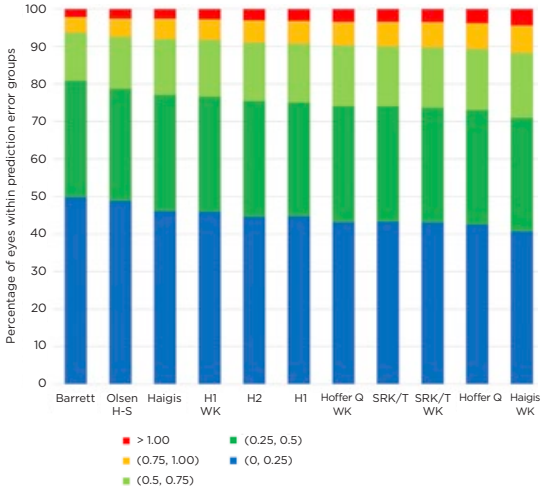
- the SRK/T formula was the most affected in eyes with flat or steep keratometry;
- with the Hoffer Q and Olsen formulas, there was significant bias with varying anterior chamber depth;
- the Haigis formula was most affected by variations in lens thickness; and
- the Wang–Koch modification of axial length for long eyes overcorrected some eyes, leading to myopic errors.

What about other IOLs? The authors cautioned that their findings might not be generalizable to other IOLs, as the lenses used in this study have the same design (anterior asymmetric biconvex) and are from the same manufacturer.

"But as these are 2 of the most commonly used IOLs in the United States, this is definitely relevant to people outside our organization," said coauthor William J. Chang, MD, also at the Redwood City Kaiser Permanente. "If we can guide [our colleagues] by saying the Barrett II does seem to be the best for these 2 lenses, it would simplify their lives as surgeons." —*Linda Roach*

1 Melles RB et al. *Ophthalmology.* Published online Sept. 23, 2017.

Relevant financial disclosures—Drs. Chang and Melles: None.



OUTCOMES. *This stacked histogram compares the percentage of cases within a given diopter range of predicted spherical equivalent refraction outcome for selected formulas and the AcrySof IQ IOL. (H1 = Holladay 1; H2 = Holladay 2; H-S = Haag-Streit; WK = Wang–Koch.)*

WORLD HEALTH

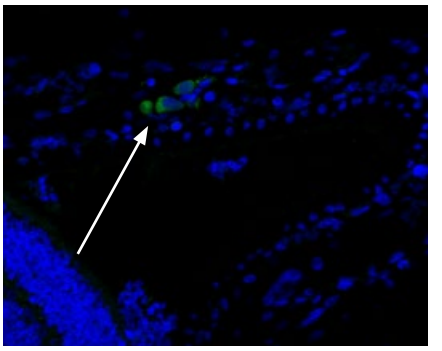
Widespread Impact of Zika on the Eye

RESEARCHERS AT THE BASCOM Palmer Eye Institute in Miami have discovered the extensive reach of the Zika virus (ZIKV) inside the eye, the totality of which suggests possible increased risks for glaucoma, uveitis, and retinal atrophy.[1]

The cellular level. For this observational case series, the researchers evaluated thin samples of ocular issue from 4 deceased fetuses previously diagnosed with congenital Zika syndrome (CZS) at the National Institute of Health in Colombia. Using scanning laser confocal microscopy and immunostaining with a ZIKV protein antibody, the team identified—for the first time—the viral localization within ocular tissue. They found remnants of the virus in the iris, neural retina, choroid, and optic nerve.

In addition, the researchers identified a number of changes, including thinning of the retinal pigment epithelium and choroid, optic atrophy, immature anterior chamber angles, and chronic inflammation.

"Unlike conventional histology with dyes, scanning laser confocal microscopy allowed us to assess—to a much finer degree—exactly what cell types the virus was infecting," said Richard K. Lee, MD, PhD. "Knowing these affected cell types can allow us to put together a pathophysiological explanation for ZIKV infection and how it causes vision and eye problems."



ZIKV. *Positive ZIKV immunofluorescence staining of cells (arrow) within the choroid.*

Informing care. "This more complete understanding of the histology of CZS also suggests that, for infected patients, ophthalmologists should examine specific aspects of the eye for increased risk of ocular disease," said Dr. Lee. They should be especially careful to look for the following.

Retinal disease. Any thinning of the retinal pigment epithelium and choroid along with loss of pigment in the patient could be a precursor to more significant retinal disease in the future, including retinal atrophy.

Glaucoma. The presence of congenital pupillary membranes and immature anterior chamber angles with ZIKV particles present in the optic nerve might suggest a greater risk of developing glaucoma.

Uveitis. Ophthalmologists should also be on the lookout for ZIKV particles in blood vessels. Along with pupillary membranes and inflammatory ocular changes, these findings might serve as a marker for increased risk of virally induced uveitis.

The Bascom Palmer team has plans to continue their research on CZS to aid in future treatment approaches, including vaccine development and pharmacotherapy. —*Mike Mott*

1 Fernandez MP et al. *JAMA Ophthalmol.* Published online Sept. 21, 2017.

Relevant financial disclosures—Dr. Lee: None.

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

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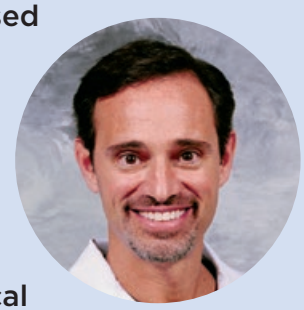

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Home Monitoring to Detect Rapid Visual Field Decline

December 2017

Recent technologic advancements have allowed patients to monitor their central visual field (VF) at home with portable devices. **Anderson et al.** investigated whether the greater test frequency afforded by home monitoring improves early detection of rapid VF loss in patients with glaucoma. They found it beneficial for this purpose, even if patient compliance is imperfect.

This computer simulation study included 43 patients who were being treated for glaucoma (open- or closed-angle), had ocular hypertension, or had suspected glaucoma. Series of VFs (n = 100,000) were simulated for those patients with stable glaucoma and for those with progressing glaucoma for 2 in-clinic schedules (yearly and every 6 months) and 3 home-monitoring schedules (monthly, fortnightly, and weekly), each lasting 5 years.

To simulate reduced compliance, the researchers randomly omitted varying percentages of home-monitored fields and manipulated the variability of the home-monitored VFs. Previously published variability characteristics were used for perimetry, and their appropriateness for home monitoring was confirmed by measuring the device's retest variability at 2 months among the study group. The criterion for determining progression was a significant slope of the ordinary least-squares regression of a simulated patient's mean deviation data.

In the clinic, sensitivity of 0.8 for rapid VF loss was achieved by 2.5 years of semiannual testing, while the same level of sensitivity was attained by 0.9 years with weekly home monitoring, despite only moderate compliance (63%) with the schedule. The superiority of weekly home monitoring over in-clinic testing every 6 months remained even when home monitoring was assumed to produce more variable test results or to be associated with low patient compliance.

Although the cost-benefit of home monitoring was not evaluated, this approach likely would reduce health resource utilization by decreasing the frequency of in-clinic testing, the researchers said.

OCT Predictors of Progression to Dry Atrophic AMD

December 2017

Certain patterns on spectral-domain optical coherence tomography (SD-OCT) have been linked to subsequent atrophy on color photography images from patients with age-related macular degeneration (AMD). Using SD-OCT findings from a previous study, **Sleiman et al.** sought to determine risk factors for new-onset geographic atrophy (GA) and central GA. They found that abnormal thinning volume of the retinal pigment epithelium (RPE) drusen complex was a strong predictor, as were atrophy or absence of the RPE layer.

For this prospective longitudinal study, the researchers evaluated a subset of patients from the Age-Related Eye Disease Study 2 (AREDS2). All 317 patients (317 eyes) in the study had bilateral large drusen or noncentral GA and at least 1 eye without advanced AMD. Baseline qualitative and quantitative SD-OCT variables were captured using standardized grading and semi-automated segmentation, respectively. Up to 7 years later, annual outcomes were extracted and were analyzed to fit multivariate logistic regression models, from which a risk calculator was derived.

Among 292 eyes with no advanced disease on baseline color photography, 46 (15.8%) developed central GA during the follow-up period (median, 4.0 years). Age-adjusted predictors determined from SD-OCT findings were abnormal thinning of the RPE drusen complex volume, intraretinal fluid or cystoid spaces, hyperreflective foci, and atrophy or absence of the RPE layer. Among the 265 eyes with no evidence of GA on baseline photography, 70 (26.4%) developed new-onset GA during follow-up (median, 4.1

years). Independent predictors were hyperreflective foci, RPE layer atrophy/absence, choroid thickness in the absence of subretinal drusenoid deposits, photoreceptor outer segment loss, volume of the RPE drusen complex, and abnormal thinning of the volume of this complex. The models yielded a calculator capable of computing risk probability of new-onset and central GA within 1 to 5 years.

The authors concluded that this risk-assessment model may simplify SD-OCT grading and, with future validation, could become a clinical prognostic tool. An online version of their calculator is available and will be updated as appropriate.

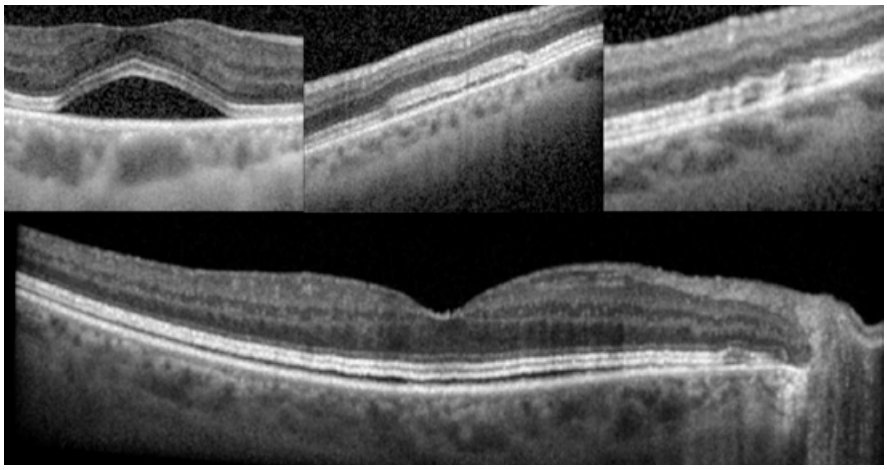
Ocular Side Effects of MEK Inhibitors: Fluid Foci

December 2017

Francis et al. studied the characteristics of serous retinal disturbances in patients who receive the class of drugs known as mitogen-activated protein kinase (MEK) inhibitors. They found that certain features distinguish these disturbances from those noted in central serous chorioretinopathy (CSC), even though the conditions have been considered analogous by some researchers.

For this retrospective single-center study, the researchers included 313 fluid foci from a total of 25 patients (50 eyes) who were receiving MEK inhibitors to treat metastatic cancer. All eyes had evidence of serous retinal detachment, confirmed by optical coherence tomography (OCT). The researchers assessed the presence or absence of subretinal fluid via clinical examination and OCT, and they evaluated the morphology, distribution, and location of fluid foci serially for each eye.

Two independent observers measured choroidal thickness at 3 time points (baseline, fluid accumulation, and fluid resolution). Statistical analysis was used to correlate interobserver findings and to compare choroidal thickness and visual acuity at each time point. OCT characteristics of retinal anomalies at baseline were compared with those at fluid accumulation.



FLUID FOCI CONFIGURATIONS. *Domes (upper left) appear as dome-shaped fluid accumulation between the RPE and the interdigitation zone. Caterpillar foci (upper middle) appear as straight or plateaued low-lying accumulations. Wavy foci (upper right) present as a linear collection of tiny domes and displace the interdigitation zone in a wave-like pattern. Splitting foci (lower) appear as a broad, low-lying accumulation of fluid between the RPE and the interdigitation zone.*

Most patients (92%) had bilateral fluid foci, which is less common in CSC. Most fluid foci in this study (77%) were multifocal, with at least 1 focus involving the fovea (83%). All fluid foci occurred between the interdigitation zone and an intact retinal pigment epithelium (RPE). Regarding morphology, the 313 fluid foci were classified as follows: dome (n = 231; 73.8%), caterpillar (n = 36; 11.5%), wavy (n = 31; 9.9%), and splitting (n = 15; 4.8%). Best-corrected visual acuity at fluid resolution did not differ significantly from that at baseline, and no eye lost more than 2 Snellen lines from baseline to fluid accumulation.

Choroidal thickness was similar at the 3 time points. Interobserver correlations were strong for choroidal thickness measurements and morphology grading. Contrary to typical CSC findings, the retinal pigment epithelium and choroid remained normal during MEK inhibition. There was no irreversible loss of vision and no serious eye damage.

The authors concluded that the subretinal fluid foci caused by MEK inhibition appear clinically and morphologically unique, and they noted that large prospective studies with greater imaging frequency are needed to draw firm conclusions.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Use Straylight to Plan Cataract Surgery in Retinal Dystrophy Patients

November/December 2017

The presence of cataracts often aggravates the visual disability experienced by patients with retinal dystrophies such as retinitis pigmentosa (RP). However, the question of whether to proceed with cataract surgery in these patients has not had a clear answer; evidence has suggested that although they may report improved visual function following cataract surgery, their postoperative visual acuity does not necessarily improve.

As a result, **van Bree et al.** set out to investigate factors that may predict visual outcomes in patients with RP and other retinal dystrophies who undergo cataract surgery. They found that straylight (disability glare) was the only parameter whose preoperative value could be used to support and thus improve the chance of a beneficial postoperative outcome.

For this prospective study, the researchers evaluated 16 patients (25 eyes) with retinal dystrophy and cataract. The patients' average age was 50 years (range, 28-71 years), and 10 of the

16 had RP. As for cataract type, posterior subcapsular cataracts dominated, observed in 20 of the 25 eyes.

The patients' corrected distance visual acuity (CDVA), spatial contrast sensitivity, and straylight were assessed pre- and postoperatively, and straylight values were compared with reference values derived from studies of healthy young eyes. Retinal function was assessed with Goldmann visual field and temporal contrast sensitivity testing, and central retinal structure was assessed with optical coherence tomography and fundus autofluorescence. Patients also completed questionnaires on visual function before and after surgery.

Straylight improvement was found in 72% of eyes postoperatively. The average straylight value was 1.75 preoperatively and 1.45 postoperatively —7.1 and 3.5 times higher than values observed in healthy young eyes, respectively.

In contrast, postoperative CDVA improved in only 20% of eyes. The postoperative CDVA measurements could not be explained by the postoperative presence or progression of maculopathy, as macular structure and function remained stable, the authors reported. They concluded that cataract surgery in patients with retinal dystrophy and early cataract may be beneficial because it significantly reduces glare disability, despite its more limited benefits with regard to CDVA. In addition, they recommended that a cut-off value for straylight of log(s) ≥ 1.66 be used as an indication criterion for cataract surgery. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Uveitis and Blau Syndrome: Preliminary Findings

December 2017

Blau syndrome, a rare autoinflammatory disease that can be debilitating, usually presents as a triad of uveitis, arthritis, and dermatitis. **Sarens et al.** are studying the course of Blau syndrome in a prospective multicenter interventional case series. Preliminary findings of their international 5-year study showed that many patients experience severe ocular morbidity despite continuous immunomodulatory therapy.

Preliminary findings were reported for 49 patients (75 eyes), each with follow-up for 1-3 years. Ophthalmic data were obtained at baseline and annual visits.

The median age at onset of Blau syndrome was 60 months, and the duration of eye disease at baseline was 145 months. In addition, 38 patients (78%) had uveitis at baseline, with 37 of the 38 experiencing bilateral involvement. Eighteen of 66 eyes (the number for which information was available) had moderate or severe visual impairment at baseline, and panuveitis was found in 38 of the 75 eyes (51%). The most common signs of optic nerve involvement were optic disc pallor (9 eyes; 12%) and peripapillary nodules (9 eyes; 12%). Of the 49 patients, 31 (63%) manifested all 3 classic features of Blau syndrome.

Active anterior chamber inflammation was observed in 30 of the 75 eyes (40%). Panuveitis was associated with longer duration of disease. At baseline, 56 of all eyes (75%) were on topical corticosteroids. Twenty-six patients received a combination of systemic corticosteroids and immunomodulatory therapy. Despite prolonged treatment in all patients, there was no significant decrease of inflammatory activity from baseline to the yearly exams; at year 3, active inflammation was evident in 11 of 18 eyes (61%).

These findings emphasize the need for frequent ophthalmologic surveillance and effective treatments in affected patients, the authors said. Greater understanding of the downstream effects of NOD2 mutations may be instrumental in the development of targeted therapies. *(Also see related commentary in the same issue by Gary N. Holland, MD.)*

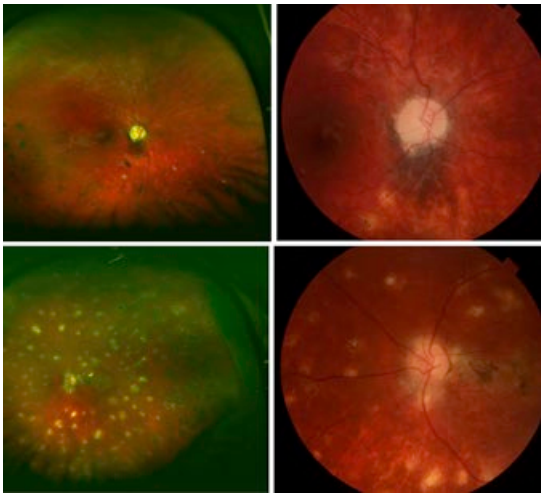
Tocilizumab for Noninfectious Uveitis: 6-Month Outcomes of STOP-Uveitis

December 2017

Sepah et al. reported 6-month safety and efficacy outcomes for 2 doses of intravenous (IV) tocilizumab administered to patients with noninfectious intermediate uveitis (NIU). Both doses were efficacious and well tolerated.

STOP-Uveitis is a randomized open-label trial of the safety, efficacy, and bioactivity of tocilizumab that is currently underway at 5 centers in the United States. Thirty-seven patients with NIU were assigned to receive an IV infusion of tocilizumab 4 mg/kg (group 1) or 8 mg/kg (group 2). Infusions were given every 4 weeks through month 6. Main outcome measures were the incidence and severity of systemic and ocular adverse events from baseline through month 6. Secondary outcomes were mean changes in visual acuity (VA), vitreous haze (VH), and central macular thickness (CMT) during the same period.

Of the patients with potential for a 2-step decrease in VH, a mean of 44%



BLAU SYNDROME UVEITIS. *Widefield fundus (left set) and optic disc fundus (right set) images from 2 patients with Blau syndrome uveitis. In the first patient, chorioretinal scars are evident in the inferior retina (top left photograph), and the pale optic disc has a nodular border (top right). Images from the second patient show multiple chorioretinal scars (bottom left) as well as peripapillary nodules around the border of the optic disc and a macular scar (bottom right).*

achieved this by 6 months (40% in group 1; 46% in group 2). By month 6, the mean change in CMT was –83.88 ± 136.1 µm (–131.5 ± 41.56 µm in group 1; –38.92 ± 13.7 µm in group 2). The mean change in VA was 8.22 ± 11.83 ETDRS letters (10.9 ± 14.6 in group 1; 5.5 ± 7.8 in group 2). There were no significant differences in efficacy or safety between the doses. The safety profile of IV tocilizumab was similar to that in other studies, and no new safety signals were detected. The higher dose was associated with 2 cases of neutropenia. (The neutropenia resolved subsequently in 1 patient, who was continued on the study medication.)

The authors concluded that both doses of IV tocilizumab (4 mg/kg and 8 mg/kg) are safe and effective in patients with NIU, and they noted that the drug may help achieve the overall goal of preventing recurrence or attaining quiescence.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Time Spent by Ophthalmologists on EHRs

November 2017

Although electronic health records (EHRs) have multiple advantages in clinical practice, many physicians see them as an obstacle to productivity. In a study of EHR use among ophthalmologists, **Read-Brown et al.** found that a substantial portion of time spent with patients is indeed devoted to EHRs.

This study entailed 2 types of research: time motion and data analytics. In the time-motion phase, manual observation was used to compare time spent on the EHR with that spent on patient conversation and examination. In the data analytics phase, EHR time stamps were used for large-scale determination of the time spent on EHRs both during and after patient visits. All 27 participating ophthalmologists (10 women, 17 men) had a standard clinical practice at the Casey Eye Institute of Oregon Health & Science University in Portland.

The mean total time spent during each patient encounter was 11.2 minutes (standard deviation [SD], 6.3 minutes). Of that, 3 minutes were devoted to EHR use (27% of the visit time), 4.7 minutes to conversation with the patient (42%), and 3.5 minutes to the examination (31%). The ophthalmologists' mean total per-encounter EHR time was 10.8 minutes (SD, 5.0 minutes; range, 5.8-28.6 minutes). Overall, 3.7 hours of each full clinic day was spent on EHRs (2.1 hours during the encounter, 1.6 hours at other times). Linear mixed-effects models demonstrated a positive correlation between EHR use and billing level and a negative correlation between per-encounter EHR use and clinic volume.

The findings emphasize the importance of creating EHR systems that meet the needs of patients and physicians, the authors said. *(Also see related commentary by Michael V. Boland, MD, PhD, in the same issue.)*

Ranibizumab and Verteporfin Photodynamic Therapy for PCV

November 2017

Polypoidal choroidal vasculopathy (PCV) is a type of exudative age-related macular degeneration common to Asians. In the 2008 EVEREST study, ranibizumab plus verteporfin photodynamic therapy (vPDT) was more efficacious than ranibizumab monotherapy in diminishing polypoidal lesions within 6 months. In EVEREST II, **Koh et al.** investigated longer-term outcomes of these treatments in a large Asian population with PCV. They found that, at 12 months, combination therapy continued to be superior to ranibizumab monotherapy for improving vision and resolving polyps.

In this double-masked multicenter clinical trial, Asian adults with symptomatic macular PCV were assigned randomly to receive intravitreal ranibizumab 0.5 mg with either vPDT (n = 168) or sham PDT (n = 154). Demographic data were similar for the study groups. Ranibizumab injections were administered on day 1 and at months 1 and 2. vPDT or sham PDT (5% dextrose solution) was given on day 1. In both groups, treatments were followed by pro re nata regimens. Main outcome variables were changes in best-corrected visual acuity from baseline to 12 months and effects on polyp regression, as assessed by indocyanine green (ICG) angiography.

At 12 months, mean improvement from baseline to month 12 was 8.3 letters for patients on combination therapy and 5.1 letters for those on monotherapy (mean difference, 3.2 letters), denoting noninferiority as well as superiority of the combined therapy. Complete absence of a polypoidal lesion on ICG angiography by month 12 occurred in 69.3% of patients on dual therapy and only 34.7% of patients on ranibizumab alone. The median numbers of ranibizumab injections were 4 and 7, respectively. Safety profiles were comparable for the 2 study groups.

In conclusion, as ranibizumab plus vPDT was superior to ranibizumab monotherapy, the authors said that combination treatment warrants consideration for patients with PCV. Because dual therapy entails fewer injections overall, it has potential to reduce the costs and overall burden of treatment. *(Also see related commentary by David J. Browning, MD, PhD, in the same issue.)*

Opioid Prescribing Patterns of Ophthalmologists

November 2017

Drug overdose is a leading cause of death among American adults, and the abuse of prescription opioids is a growing public concern. **Patel and Sternberg** looked at the role of ophthalmologists in the opioid abuse epidemic. They found that most practicing ophthalmologists use discretion in prescribing opioids to their patients.

For this study, the researchers collected Medicare Part D prescriber data pertaining to opioid drugs for all participating ophthalmologists from 2013 to 2015. Documented details included the number of original prescriptions and refills, the number of days' supply, and prescribing rates. The mean annual number of opioid prescriptions written by ophthalmologists was calculated and

compared with the number of overall prescriptions issued. The researchers also noted the geographic distribution of the opioid prescriptions.

The number of ophthalmologists varied by study year from 19,587 to 19,712. Although most (88%-89%) issued 10 or fewer opioid prescriptions each year, approximately 1% wrote more than 100 such prescriptions annually (mean supply, 5 days); this remained constant for each year of the study. Nearly half of ophthalmologists did not issue any opioid prescription or refill during the study period (44% in 2013 to 49% in 2015). The mean number of opioid prescriptions written by ophthalmologists, including refills, was similar for the 3 years.

Among the ophthalmologists who wrote more than 10 opioid prescriptions each year, these drugs represented only 8% (mean) of their total annual prescriptions. Geographically, Alabama, Arkansas, Georgia, Oklahoma, Tennessee, and Texas had the highest volume of opioid prescriptions, while Alaska, Iowa, New Jersey, North Dakota, South Dakota, Vermont, and Wyoming had the lowest volume. The District of Columbia also was a low-volume location.

The authors noted that advancements in ophthalmic surgery may contribute to the relatively fixed opioid prescribing rates in ophthalmology as opposed to the rising rates in other surgical specialties. Even so, they cautioned, "the current epidemic highlights the substantial risk of opioid dependency even with seemingly innocuous prescribing patterns."

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Optic Nerve Infiltration in Primary CNS Lymphoma: Presentation and Outcome

JAMA Neurology
Published online October 2, 2017

Optic nerve infiltration (ONI) is a rare presentation of primary central nervous system lymphoma (PCNSL). To better understand lymphomatous ONI, **Ahle et al.** retrospectively reviewed data for affected patients. They found that visual and systemic prognosis was poor, even if neuroimaging showed a response to chemotherapy.

The authors examined databases of 3 French hospitals for a 17-year period and identified 752 cases of PCNSL. Lymphomatous ONI was documented for 7 of them, and data were collected from medical records, including clinical presentation, neuroimaging results, and biological features. Treatment response was assessed clinically and by follow-up magnetic resonance imaging (MRI), utilizing response criteria of the International PCNSL Collaborative Group.

The median age at diagnosis was 65 years (range, 49-78 years). Five of the 7 patients were female. Two patients had ONI at initial diagnosis of PCNSL, and 5 experienced ONI during disease relapse after chemotherapy. In all 7 patients, ONI was characterized by subacute severe visual impairment that progressed rapidly. MRI scanning of the optic nerve showed contrast enhancement in all 7 patients and thickening in 3 of them. Additional lesions were observed in 4 patients. Lymphomatous meningitis was detected from cerebrospinal fluid in the 2 patients with ONI at initial presentation.

At follow-up (median, 13 months), 5 patients had persistent severe low visual acuity or vision loss, and 2 patients exhibited partial recovery. The median progression-free survival time after ONI identification was 11 months; the median overall survival period was 18 months.

In conclusion, lymphomatous ONI is a rare condition involving rapid severe visual loss and poor optic nerve function, even in patients whose disease responds to chemotherapy. Early diagnosis, which can be difficult in the absence of cerebral lesions or meningitis, along with prompt treatment can improve the visual prognosis.

Vision Screening in Young Children: Evidence Review

JAMA
2017;318(9):845-858

Untreated amblyopia, strabismus, and nonamblyopic refractive error can lead to bullying, poor academic performance, and reduced quality of life. In 2011, the U.S. Preventive Services Task Force recommended screening for these conditions and their risk factors in 3- to 5-year-olds. In an effort to provide updated information to the task force, **Jonas et al.** reviewed recent evidence on the effectiveness and safety of such screening in children aged 6 months to 5 years. They found that, although direct data are limited and inconclusive, indirect evidence supports testing of preschoolers at risk for vision problems.

The authors searched primary databases for English-language articles published from January 2009 through June 2016 and reviewed clinical trial registries. Among the 40 studies analyzed (34,709 children), 34 involved assessment of test accuracy. Positive likelihood ratios for amblyopia risk factors or refractive error were moderate (5-10) in most studies but higher (> 10) in studies involving multiple clinical tests. Test accuracy did not differ by age group. The most common difficulty related to screening was false-positive findings, with higher rates (usually > 75%) in studies with a low prevalence (< 10%) of vision abnormalities.

After 5-12 weeks of treatment, patching improved visual acuity by a mean of < 1 line on a standard chart in children with amblyopic risk factors who were pretreated with eyeglasses. Children who were patched were more likely to improve ≥ 2 lines than those who weren't (45% vs. 21%, respectively). By 1 year, compared with no treatment, patching plus eyeglasses improved visual acuity by approximately 1 line in children not pretreated with eyeglasses, whereas eyeglasses alone improved it < 1 line. None of the reviewed studies addressed the effects of treatment on school performance, functioning, long-term amblyopia, or quality of life, and none established whether vision screening in preschoolers is beneficial.

The authors acknowledged that inability to cooperate may limit the use of some tests in children who are younger than 3 years of age.

—Summaries by Lynda Seminara

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Monitoring Flattening After CXL for Keratoconus

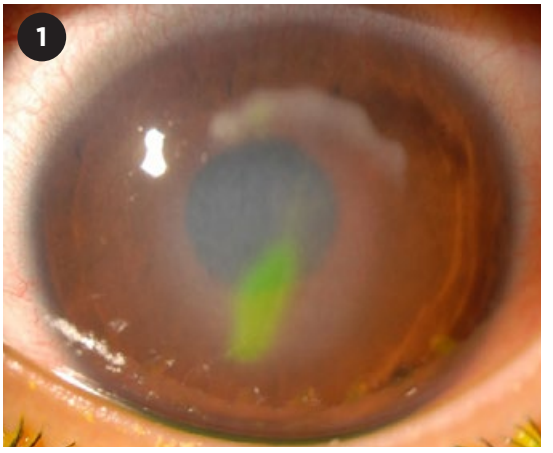
Clinical studies have shown that corneal cross-linking (CXL) is an effective treatment to strengthen the cornea and reduce progression in patients with keratoconus.[1-3] However, in rare cases, intense corneal remodeling occurs after the procedure, according to Marcony R. Santhiago, MD, PhD, who holds appointments in the United States and Brazil. By comparison, the majority of patients have stable readings after the procedure or flattening of up to 1 D or 2 D over 2 years.[4]

Case reports. Dr. Santhiago described 2 cases of significant corneal flattening and remodeling 1 year after a standard CXL protocol.[4]

- A 28-year-old woman with progressive bilateral keratoconus was treated in the right eye only. The maximum keratometry (Kmax) in that eye had increased more than 1.0 D during the previous year, and her preoperative steep and flat keratometric readings in the right eye were 59.74 D and 51.94 D, respectively. One year after treatment with standard epithelium-off CXL (3 mW/cm^2 for 30 minutes, with a total energy of 5.4 J/cm^2), her steep and flat keratometry readings had dropped to 48.80 D and 45.9 D, respectively (a decrease in the differential map of 14 D).
- The second case was a 14-year-old boy with progressive bilateral keratoconus whose right eye was treated. As with the first patient, that eye had demonstrated progression of more than 1.0 D during the previous year. His steep and flat keratometry readings were 63.26 D and 52.91 D, respectively, before he underwent standard epithelium-off CXL. One year later, his steep and flat keratometry readings changed to 56.76 D and 50.40 D, respectively (a decrease in the differential map of approximately 7 D).

Neither patient experienced complications during or immediately after treatment. One year after CXL, both tolerated a gas-permeable contact lens, achieving a corrected distance visual acuity (VA) of 20/25 in the treated eye.

William B. Trattler, MD, of the Center for Excellence in Eye Care in Miami, who has performed CXL continuously over 9 years as part of 2 studies (Peshke, CXLUSA), explained that patients who experience intense corneal reshaping usually have greatly improved vision, as was reported in these 2 cases. "You're starting off with patients who have advanced keratoconus," he said. "They have very irregularly shaped corneas. The corneal remodeling resulted in significant reshaping and flattening over the first year following CXL, so the patient's cornea and vision are moving in the right direction. One expects that with more time, these 2 patients will experience further corneal reshaping."



POSTOP. *Five days after epithelium-off CXL, this patient's eye shows corneal inflammation and a delay in epithelial healing.*

William B. Trattler, MD

Further investigation. Dr. Santhiago continues to study additional cases with intense flattening after standard CXL. Cases such as these raise questions in the refractive surgery community. What physiologic processes are taking place in these eyes? What are the main preoperative factors associated with intense corneal remodeling after CXL? What does this mean for treatment going forward? The conversation is just beginning, with much still to be learned.

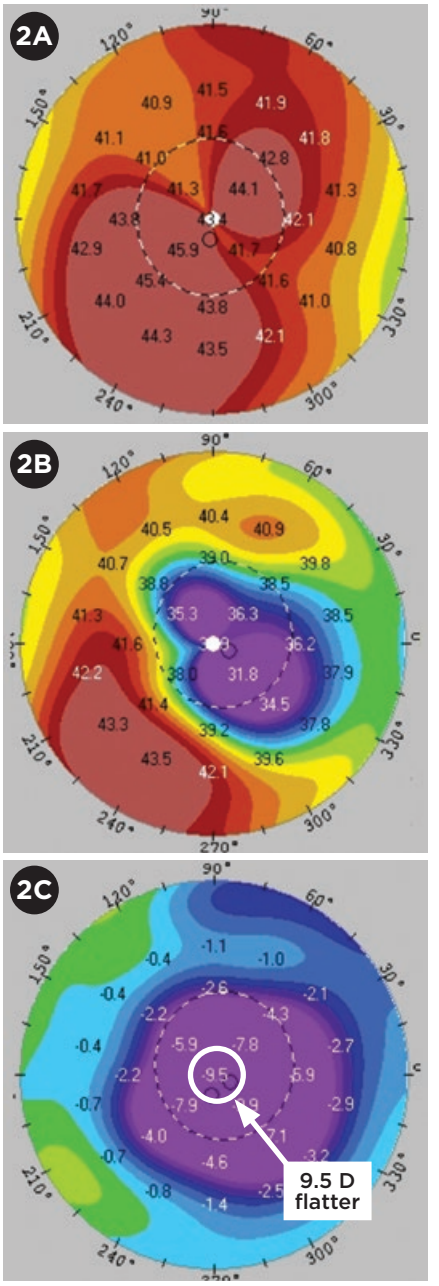
Implications

What are the implications of intense flattening?

Physiologic processes. "First, this flattening reveals that there is a potent ongoing remodeling effect in the year after the surgery, and it indicates that there are gradual viscoelastic adjustments in response to the altered distri-

BY DIANE DONOFRIO ANGELUCCI, INTERVIEWING **VIRIDIANA KOCABA, MD, MARCONY R. SANTHIAGO, MD, PHD,** AND **WILLIAM B. TRATTLER, MD.**

Eye: OS	UCVA	BCVA	Refraction
Preop	CF	25	-6.75 + 3.25 x 35
3 Months Postop	400	200	-3.75 + 3.50 x 40
9 Months Postop	400	30	-6.00 + 2.50 x 45



COMPARISON OF PATIENT'S LEFT EYE. *(2A) Preoperative topography, (2B) 9 months postoperative topography, and (2C) difference map. At 3 months post-operatively, there was a significant reduction in vision due to corneal haze. Topical steroids were used. At 9 months postoperatively, the haze had improved. The cornea demonstrated significant corneal flattening.*

bution of stress imposed by selective stiffening of the cornea relative to the adjacent sclera," Dr. Santhiago said. "The corneal remodeling, in general, after CXL is probably related, among other things, to intense wound healing, an increase in corneal elasticity, CXL effective depth, and central cone location," he said.[5-7]

"This flattening process appears to slowly continue over the years,[8] which supports the hypothesis of the long-term effect of CXL," said Viridiana Kocaba, MD, at the Université Claude Bernard Lyon 1, Edouard Herriot Hospital in Lyon, France.

Dr. Trattler added, "We have patients who have significant corneal reshaping without corneal haze that continues over many years. With continued improvement in corneal shape, patients can typically experience improvement in quality of vision over time."

Clinical. The clinical ramifications include the following:

Patient selection. A careful preoperative selection of patients is recommended, said Dr. Kocaba. Like other surgical procedures, this decision is based on the balance between benefits and risks, she said, adding that it is important not to underestimate the potential risks and that additional prospective studies are needed to increase selection criteria. Specifically, she pointed out that research such as that by Koller et al. found that preoperative Kmax exceeding 54.0 D was associated with statistically significant corneal flattening during the first year after CXL.[9] And Dr. Santhiago said that he's observed that children's corneas tend to have more dramatic flattening, but he noted that more data are needed to corroborate this perception.[4]

Along similar predictive lines, Dr. Santhiago added, "One of our studies is revealing that, although [they are] only mild predictors, the preoperative flat keratometry and the difference between flat and steep keratometry may be some of the indicators of how much that cornea will remodel or flatten."

Likewise, Dr. Trattler explained that preoperative levels of disease severity can influence the response. "If you have somebody who has mild keratoconus, they will only have a modest amount of corneal flattening," he said. "If you have someone who has a severe level of keratoconus, they're more likely to have a more significant response to the treatment."

Postop care. "These reported cases underline the absolute necessity of a close follow-up of our patients after CXL," Dr. Kocaba said. After CXL, she usually sees patients at days 1 and 7 and months 1, 3, and 6, depending on the result. If the eye is stable, she sees the patient every 6 months thereafter. Dr. Santhiago added that some studies have shown that the flattening process can continue for 5 years. In fact, Kymionis et al. reported the case of a 23-year-old woman with bilateral CXL who experienced significant flattening and thinning of the cornea in the right eye throughout a 5-year follow-up period while the left eye remained stable.[10]

Dr. Kocaba noted that excessive corneal flattening after CXL may be associated with deep stromal haze[10] or a significant decrease in corneal thickness.[11] Dr. Trattler spoke of a patient who experienced inflammation of the cornea in the early postoperative period following epithelium-off CXL (Fig. 1). "The patient was treated with topical steroids for the inflammation. However, the patient developed corneal haze and experienced significant corneal flattening," he said. "While the haze improved over time, the patient still had mild corneal haze along with significant corneal flattening, which resulted in slightly reduced vision compared to the patient's vision prior to epi-off CXL."

In light of these potential changes, Dr. Santhiago suggested that any subsequent refractive procedure be delayed until remodeling has occurred. "I believe either contact lens—scleral or not—or intracorneal ring segments [ICRS] are

William B. Trattler, MD

better planned at least 1 year after the surgery."

A positive? On the flip side, Dr. Santhiago and Dr. Trattler agreed that the intense remodeling has a positive effect in some corneas when there is no need for topography-guided excimer laser procedures or ICRS.

But Dr. Kocaba pointed out, "Even if corneal flattening seems to be a positive side effect, these cases of intense flattening highlight the possible unpredictable response of the cornea after CXL."

Ongoing Research

Ophthalmologists need to continue investigating the cases in which intense flattening occurs.

Biomechanical data needed. "The indication for CXL is currently based on only one tool—corneal topography," Dr. Kocaba said. "Changes in corneal topography are still insufficient to provide conclusive evidence of keratoconus progression. That is why corneal biomechanical and biochemical changes might need to be included in this decision. Indeed, understanding biomechanical destabilization of the cornea could probably assist with the management of the keratoconus."

She added, however, that the processes underlying corneal biomechanical changes after CXL are unclear. Previous studies have shown that while biomechanical properties after ex vivo CXL suggest corneal stiffness, these findings may not be accurate indicators of the in vivo response to CXL.[12]

"Several in vivo measurements of corneal biomechanics have been developed, such as supersonic shear wave imaging, applanation resonance tonometry, acoustic radiation force, and scanning acoustic microscopy," she said. These are being studied experimentally.

Confocal microscopy might help. "A progressive reduction in collagen corneal keratocytes has been observed in patients with keratoconus, and the decline in keratocyte density correlates with indices of disease severity," Dr. Kocaba said.[13] In addition, she said, activated keratocytes increase after CXL, possibly indicating greater stromal inflammation.[14] She suggested that in vivo confocal microscopy could help identify patients at high risk of intense flattening after CXL.[15]

Improving Results

As research continues, Dr. Trattler offered recommendations to help ophthalmologists obtain optimum results.

Evaluations. Clinicians need to evaluate key factors in patients with keratoconus, such as uncorrected VA, best-corrected VA, and corneal shape. "You want to be able to compare one visit to the next by looking at comparative topography maps—called difference maps," he said. At each visit, ophthalmologists can use these difference maps to determine whether keratoconus is stable or whether areas of the cornea are becoming flatter or steeper.

Technique. CXL technique is also important. "Dr. Michael Mrochen has shown that we should center the UV light overlying the thinnest part of the cornea,[16] which results in a greater effect," Dr. Trattler said. "If the thinnest part of the cornea is in the center of the cornea, and a patient is looking directly at the light, then the UV light will be centered over the thinnest part of the cornea and it will travel deeper in the cornea where the cornea is weakest. But if the thinner part of the cornea is significantly inferior to the center, then the UV light rays will hit that part of the cornea at a bit of an angle, resulting in some reflection of light. Therefore, it may help to have the patient look slightly above the UV light, so that the UV light is centered over the thinnest part of the cornea."

Looking Ahead

While Dr. Santhiago and his colleagues are currently focusing on identifying the main preoperative factors associated with intense corneal remodeling after CXL, he expects that in the future, ophthalmologists will be able to adapt CXL fluence and time according to each patient. "I am positive that we are working toward a more personalized procedure, not only in identifying the individuals who will have the most intense corneal remodeling, but also those who are going to benefit from it," Dr. Santhiago said.

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Dr. Trattler practices with the Center for Excellence in Eye Care in Miami. *Relevant financial disclosures: Avedro: L; CXLO: C,O; CXLUSA: C.*

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

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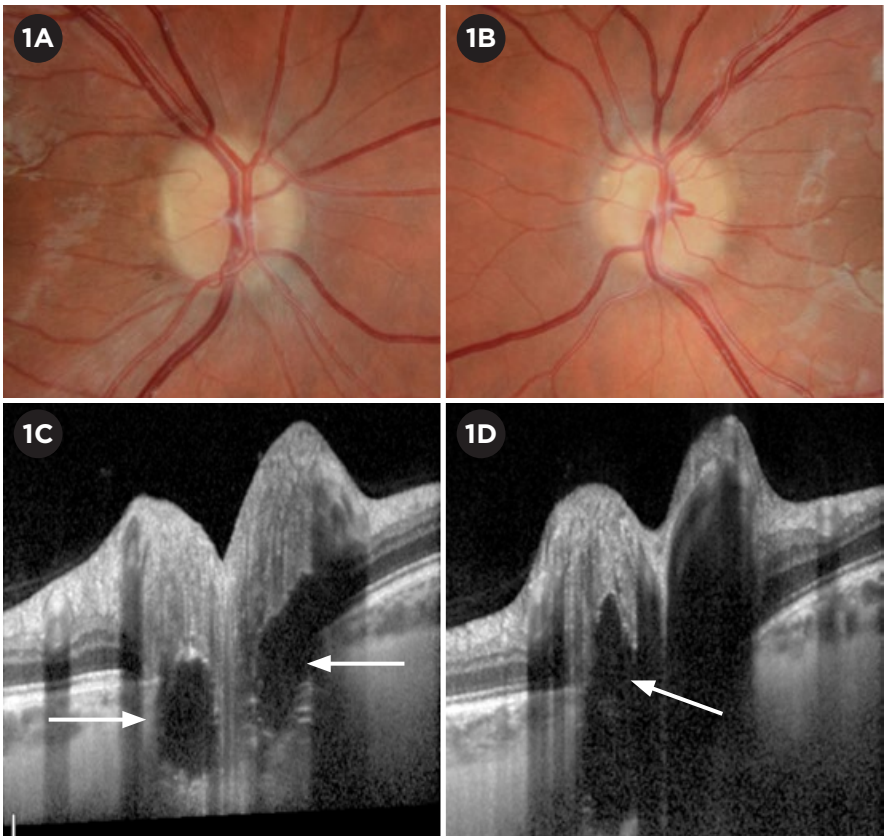
MD Roundtable: Longitudinal OCT in Pediatric Practice

Last month's issue of *EyeNet* contained part 1 of a roundtable discussion hosted by David A. Plager, MD, of Indiana University and Riley Hospital for Children. In this second installment of the 2-part series on optical coherence tomography (OCT) in pediatric patients, Dr. Plager resumes his conversation with Sharon F. Freedman, MD, of Duke University Eye Center, and Fiona E. Costello, MD, FRCPC, of the University of Calgary. The experts offer insight on incorporating OCT into the longitudinal evaluation of children with optic neuropathy.



FUNDUS AND OCT IMAGES. *A 13-year-old boy presented with bilateral optic disc elevation (1A: right eye, 1B: left eye). To rule out causes of raised intracranial pressure, he underwent a cranial MRI scan, which was normal. A lumbar puncture showed a normal opening pressure and cerebrospinal fluid constituents. (Both MRI and lumbar puncture were done by neurology.) Enhanced-depth imaging with spectral-domain OCT testing (1C, 1D) showed 2 large buried drusen in the right eye (arrows) and 1 buried druse in the left eye (arrow).*

Pediatric Glaucoma

Dr. Plager: *How do you apply OCT alongside traditional metrics for following glaucoma in children?*

Dr. Freedman: It depends on the patient. A child may be referred to me with suspected glaucoma based on visual inspection of the optic nerve, and I would use OCT to examine the amount of rim tissue in the optic nerve head via measurement of the retinal nerve fiber layer and macular thickness maps. The patient may have a large optic nerve head with a large cup and a healthy rim; in that case, a completely normal and symmetrical RNFL in both eyes would provide reassurance, along with normal eye pressures, that the cupping is physiologic. Conversely, a second patient may have a much smaller nerve with a small cup, but OCT may confirm a thin RNFL, suggesting an optic nerve damage not so easily seen on clinical examination alone.

We still lack a truly normative database of OCT values in children, and even if we had one, the range of "normal" is quite large across children of varying ages, ethnicities, and axial lengths. Nevertheless, OCT is very helpful for assessing a child with presump-

ROUNDTABLE HOSTED BY **DAVID A. PLAGER, MD,** WITH **FIONA E. COSTELLO, MD,** AND **SHARON F. FREEDMAN, MD.**

tive glaucoma but normal intraocular pressure (IOP) who is considered low risk. For such a patient, the central corneal thickness should be determined to be sure it is not abnormally thin, and the family history should be reviewed for early onset glaucoma. If the patient's parents are present, I may examine the sizes of their optic nerves and cups for comparison. In the pre-OCT days, if all these features were normal, and results of the workup otherwise were normal, I would simply monitor the patient for elevated intraocular pressure. However, being able to measure the RNFL and macular thickness, and finding the values robust and symmetric, give me much more confidence that the nerve is healthy and the cup is nonglaucomatous. OCT findings also provide a good baseline for longitudinal monitoring. If the patient's OCT results are unchanged through 1 year of follow-up, with no other features worrisome for glaucoma such as elevated intraocular pressure, I would consider the risk of glaucoma to be very low.

As an alternative example, a child with 20/20 visual acuity and no ophthalmic concerns may undergo testing at an optometrist's office and have abnormal OCT results. The scan may show an optic nerve pit or a region of the optic nerve that appears underdeveloped, and this may be accompanied by a matching visual field defect. In such cases, visual inspection of the nerve can yield crucial information; for example, it may show that the abnormality likely does not result from a progressive disease process but rather is a nonglaucomatous congenital defect of the optic nerve.

Dr. Costello: I have identified more cases of optic nerves with segmental hypoplasia by OCT than by visual examination. OCT enables detection of subtle differences in symmetry that may be missed by clinical evaluation alone.

Dr. Freedman: Consider a child who was born prematurely and has an associated morbidity of the central nervous system (CNS), such as interventricular hemorrhage, periventricular leukomalacia, and/or mild cerebral palsy. On examination, the patient has large optic nerve cups with borderline elevated IOP, and OCT findings show very low RNFL thickness in both eyes. My recommendations would be to consider that OCT result as the baseline, presume that the RNFL thickness is low because of trans-synaptic CNS damage associated with prematurity, and suggest longitudinal monitoring.

In my experience, the test-retest variability for an OCT machine is generally 5 to 6 µm. When I start to see changes in overall (mean) peripapillary RNFL measurements in excess of 5 to 6 µm—and certainly in excess of 10 µm—I would suspect pathology. I might be looking at subtle optic disc edema or subtle manifestations of atrophy.
—Dr. Costello

Dr. Costello: I agree regarding the value of longitudinal follow-up. When asked to assess a patient with an acquired optic neuropathy, I often say, "I have a snapshot, and I need a movie. Therefore, I need to collect more data points over time."

True Change

Dr. Plager: *How much change in successive OCT results do you expect to see before you regard an effect as real and not just fluctuations between scans?*

Dr. Costello: In my experience, the test-retest variability for an OCT machine is generally 5 to 6 µm.

Dr. Freedman: I agree.

Dr. Costello: When I start to see changes in overall (mean) peripapillary RNFL measurements in excess of 5 to 6 µm—and certainly in excess of 10 µm—I would suspect pathology. I might be looking at subtle optic disc edema or subtle manifestations of atrophy.

Dr. Freedman: OCT is particularly helpful in early glaucoma because a patient may lose up to 60% or 70% of the RNFL and still be preperimetric.[1,2] These data come mostly from adults but likely are true for children as well.

If you require presence of a visual field defect to confirm that glaucoma is progressing, much of the RNFL will be lost before you get a positive result. In preperimetric or early perimetric stages of glaucoma, serial OCT scans are invaluable for monitoring progression.

As the RNFL gradually is damaged and diminished—such as to a thickness of 43 µm that decreases to 41 or 38 µm by the next visit—this layer becomes too thin to monitor change reliably with OCT. At that point, visual field testing should be your preferred mode of monitoring, assuming the patient is cooperative. In my experience, patients who are at least 6 years old and cognitively normal, and who have relatively good central visual acuity and no nystagmus, can usually maintain the fixation necessary for OCT analysis, whereas many 10-year-old patients still are unable to undergo reliable visual field testing.

I agree that a global RNFL change of more than 6 or 7 µm is concerning and likely indicative of true change. However, for pediatric patients, you have to be particularly attentive to the tracing on the OCT output. I have obtained OCT results that are phase shifted from the patient's previous results, which suggested that the child moved during testing, not that the RNFL had thinned. In contrast, global thinning of the RNFL—involving, for instance, the superotemporal and inferonasal sectors—is more worrisome. As with visual field testing, the findings of repeated OCT studies are helpful for identifying change.

Dr. Costello: In follow-up for patients with a CNS demyelinating process, such as multiple sclerosis, I look for subclinical manifestations of damage to the afferent visual pathway, including sectoral or global RNFL thinning and ganglion layer loss. In general, you should obtain a high-quality scan, have a good understanding of the disease that you're following, and confirm that the results are reproducible so that you know the OCT findings are real

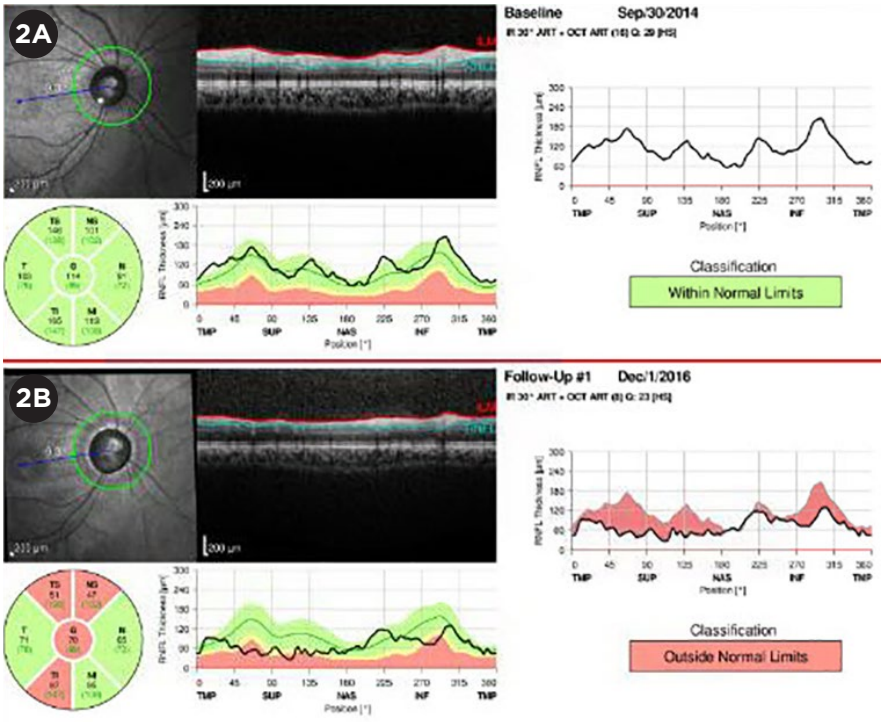
rather than artifactual.

Dr. Freedman: There also are cases in which results of RNFL thickness do not give a complete picture. For example, a uveitic eye can have subtle macular thickening and can resemble papilledema with atrophy. In Sturge-Weber syndrome, a very thick choroid can preclude or make more difficult good OCT measurements of the RNFL.

Dr. Costello: I agree. For a patient with a compressive etiology, such as pituitary adenoma, results of ganglion layer analysis may show nasal hemiretinal thinning in advance of the bitemporal hemianopsia that hasn't manifested yet (but will over time).

With OCT, you can evaluate patterns beyond those of the peripapillary RNFL to understand pathologies involving the optic nerve, the chiasm, or the tract. Some patients may even have retrogeniculate causes of vision loss, such as tumors, that can induce retrograde trans-synaptic degeneration. This degeneration yields a specific pattern of ganglion layer loss in OCT analysis that correlates with the visual field deficit. For OCT findings to be meaningful and interpretable, you need at least a fundamental understanding of the disease you're following.

In adult patients with dominant optic atrophy, OCT may show extreme thinning of the peripapillary RNFL and ganglion layer measures, but visual function by standard automated perimetry may be better than expected, possibly because of cortical adaptation. These findings (a dissociation between structure and function) may suggest a chronic process acquired in early childhood, rather than an acute ischemic or inflammatory condition acquired in adulthood.



SD-OCT COMPARISON. *(2A) This 12-year-old boy was seen initially as a glaucoma suspect with an IOP of 21 mm Hg and a healthy optic nerve; follow-up was recommended 6 months later. (2B) He did not return until 2 years later, with IOP in the high 30s in both eyes and dramatic loss of RNFL in the right eye, with cupping that worsened from 0.65 initially to a near-total cup. Aggressive management, including medications and surgery, were needed.*

Dr. Freedman: Resilience of the optic nerve varies among children with high IOP. The patient in Fig. 2 showed an unusual and asymmetric progression of optic nerve cupping and corresponding RNFL loss in the right eye over less than 2 years when his pressures rose in both eyes. In contrast, a patient with aphakia and a small optic nerve can have pressure ranging from 20 to 30 mm Hg for a very long time and still maintain normal RNFL thickness.

For pediatric patients with glaucoma who can undergo OCT, this technology gives us a way to detect subtle disease progression even when the IOP is within the target range. We can identify and treat structural loss, hopefully before the patient experiences a visual field defect. Conversely, for a patient with pressure in the low 20s, longitudinal OCT findings confirming a stable RNFL and hence a healthy optic nerve are reassuring.

For pediatric patients with glaucoma who can undergo OCT, this technology gives us a way to detect subtle disease progression even when the IOP is within the target range. We can identify and treat structural loss, hopefully before the patient experiences a visual field defect. —Dr. Freedman

Dr. Costello: For pediatric patients with suspected functional (nonorganic) vision loss, normal OCT measures obtained repeatedly over time can provide reassurance that afferent visual pathway structure is preserved. In cases of optic neuritis, OCT measures change over time, often showing progressive peripapillary RNFL thinning and ganglion layer loss. For conditions that mimic optic neuropathy, such as acquired retinal disorders in which there is a substantial visual field defect and a normal-appearing optic nerve, I would recommend OCT testing and/or electroretinography. You should consider other mechanisms for vision loss than chronic optic neuropathy in the setting of normal peripapillary RNFL and ganglion layer measures.

Dr. Freedman: Our discussion has focused on the inner retina, which is

Sharon F. Freedman, MD

what Dr. Costello and I see often, but there are times in a pediatric ophthalmology practice when you cannot get a patient's refraction where it needs to be—maybe the patient's optometrist or pediatrician couldn't either—and you have to decide if there is a functional defect. I don't necessarily trust only my opinion in such cases. I have had several patients whose OCT findings indicated early Stargardt disease, disruption of the ellipsoid zone, or early photoreceptor loss. These children unfortunately may languish as malingerers when they actually have outer retinal changes. Once we've differentiated functional deficits from real retinal problems, we can refer these patients to our retina colleagues and other support services for low vision.

Dr. Costello: That's an excellent point. Without OCT, we're often waiting for more glaring changes to emerge in results of qualitative assessments of the optic nerve. Thus, we may miss subtle preclinical manifestations of an acquired optic neuropathy. As a result, the patient's diagnosis can be delayed.

Imaging Frequency

Dr. Plager: *For a case that seems relatively stable, such as optic neuropathy or glaucoma with borderline abnormal IOP that is being managed with eyedrops, how often do you repeat OCT before you expect that you might see some change?*

Dr. Freedman: Generally, glaucoma patients in my practice undergo annual OCT testing. For some patients, I want to avoid surgery, whereas other patients have undergone surgical procedures already and we really need to know if the disease is worsening. If I see a change in imaging findings compared with the previous year or if I'm having trouble establishing whether the patient's condition is stable or warrants intervention, I will repeat OCT as frequently as every 4 months.

For high-pressure glaucoma, especially severe juvenile open-angle glaucoma, in which the RNFL has thinned to approximately 40 to 50 µm, I'll perform a procedure to decrease the intraocular pressure, and the nerve may reverse the cupping, but the RNFL will continue to thin for a bit. This phenomenon may be due to damaged and perhaps even swollen nerve fibers that continue to undergo apoptosis after the procedure, despite the pressure being lower. Unfortunately, even if you lower IOP in patients with glaucoma, damage to the RNFL does not improve.[3]

Dr. Costello: I agree. In cases like compressive optic neuropathy, I've seen progressive loss of the ganglion layer and sometimes the RNFL, even after the source of compression is removed. I think the continued loss corresponds to vulnerable axons and neurons that already were committed to a process of damage or loss, despite removal of the insult.

I can provide 3 examples of how I use OCT to monitor patients with ophthalmic conditions other than glaucoma and how I interpret changes in longitudinal results. My approach to OCT is practical.

For a patient with idiopathic intracranial hypertension, I would use results of perimetry, fundus examinations, and OCT to demonstrate beneficial effects of treatment over a series of clinic visits. If the patient has started treatment with acetazolamide, repeat OCT testing (over intervals of weeks to months) will show gradual improvement in optic nerve swelling and normalization of the peripapillary RNFL. OCT results, in conjunction with functional outcomes, guide my decision-making for tapering or increasing their medication. Rather than simply telling the patient and parents that there is Frisén grade 2 or 3 swelling of the optic nerve, I'm able to show them the structural findings over time, in a meaningful way. Moreover, I can detect subtle increases in RNFL thickness in patients with less well-controlled idiopathic intracranial hypertension, versus stability (in RNFL measurements) in patients with good disease control.

For a pediatric patient with multiple sclerosis, loss of peripapillary RNFL or ganglion layer thickness in the absence of a discrete (clinically overt) optic neuritis event is concerning because it suggests that subclinical disease activity is not being controlled sufficiently by the patient's disease-modifying therapy. In such a case, I would talk with my pediatric neurology colleague about therapeutic strategies, which may improve the patient's disease control.

For a patient with buried optic disc drusen, I would use serial OCT testing to monitor drusen size and location (superficial versus buried). In the setting of superficial optic disc drusen, I would look for evidence of subtle changes over time in the integrity of the peripapillary RNFL and the ganglion layer that might correlate with evolving visual field defects.

Use of OCT and interpretation of the results should be driven by context. To determine if a patient's condition is improving, worsening, or staying the same on the basis of OCT findings, you must have an understanding of the disease process and its underlying cause. Only then can you separate signal from noise.

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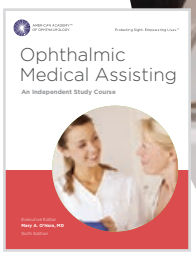

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Pterygium in Young Children

Pterygium is a benign, wedge-shaped, progressive fibrovascular overgrowth of the degenerated bulbar conjunctiva, seen most commonly on the nasal limbus (Fig. 1). The condition is often asymptomatic, especially early in its development. As a pterygium gradually encroaches toward the visual axis, it can cause astigmatism, which may be the main visual complaint.[1] In addition, the lesion may become inflamed, leading to ocular surface irritation.

Although pterygium is rare in young children, we have treated several of these patients at our medical college.

Epidemiology

Among the general population, the prevalence of pterygium varies widely, with estimates ranging from 0.3% to 29% worldwide. A meta-analysis of pooled data from 20 studies, encompassing more than 900,000 cases in 12 countries, found an overall prevalence of 10.2%, with a slightly higher rate among men than women.[2]

Pterygium occurs most frequently among people who live in tropical areas near the equator. Ultraviolet light exposure is thought to be the most likely cause, and dust, dryness, and wind are also risk factors.

The peak incidence of primary pterygium lies between the ages of 20 and 40 years; outside of that range, the condition is rarely seen in children and more commonly in persons over the age of 40 years.[3] However, the risk factors noted above can particularly affect children who play outdoors.

Pathophysiology

Numerous studies suggest a genetic predisposition to the development of pterygium. During embryological development, there may be cellular migration of keratoblasts prompted by vimentin, a type III intermediate filament protein.

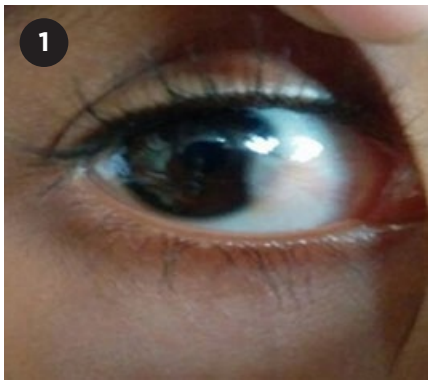
Another theory suggests that increased P53 expression, along with a paucity of tumor suppressor gene, facilitates the abnormal proliferation of limbal epithelium. Type 1 hypersensitivity is also known to play a role in the pathogenesis of pterygium.

Histology

Histopathologic examination demonstrates conjunctival mucosa lined by stratified squamous nonkeratinized epithelium with interspersed goblet cells. Compared with adults, children have an increased number of mast cells. The underlying stroma shows fibrocollagenous tissue, with areas of hyalinization and superficial congested vessels.

Clinical Presentation

The classic presentation of pterygium is a fibrovascular lesion in the palpebral fissure, originating in the nasal aspect of the conjunctiva. Typically, the growth progresses gradually and horizontally toward the limbus, cornea, and visual axis. The condition is usually bilateral.



CLINICAL APPEARANCE. *Pterygium in a young child seen at our clinic.*

The affected eye may be red, with no discharge. There may be an irritated, gritty sensation, leading to constant eye rubbing.

Refractive effects. A small pterygium has few symptoms and no harmful effects. However, as it grows, the child may complain of blurred vision due to development of refractive astigmatism, generally of the with-the-rule type. Frequent headaches may occur as a consequence of the astigmatism.

Differential Diagnosis

Pinguecula. This condition appears as a yellow-white mound or aggregation of smaller mounds on the bulbar conjunctiva adjacent to the limbus, remaining localized to the conjunctiva without involving the cornea. The histology is

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very similar to pterygium, and pinguecula often precede the development of pterygium.

Pseudopterygium. This term describes a band of conjunctiva adhering to an area of compromised cornea at its apex as a result of chemical or thermal burns, trauma, or marginal corneal disease. The lesion is not confined to the palpebral fissure. As an important point of distinction, a probe can be passed beneath a pseudopterygium near the limbus, while this is impossible in true pterygium.

Workup

The clinical diagnosis of pterygium is based on history, anterior segment slit-lamp examination, and refraction to assess for astigmatism.

Staging. Pterygium is graded according to the extent of corneal involvement.

Grade I: at the limbus

Grade II: between the limbus and the pupil

Grade III: extending to the pupillary margin

Grade IV: crossing the pupillary margin

Treatment

Management of pterygium in children is generally the same as in adults. Definitive resolution may be more difficult to achieve than it is in adults, however, because pterygium recurs more aggressively and at a reportedly higher rate of 36.1% in children.[4]

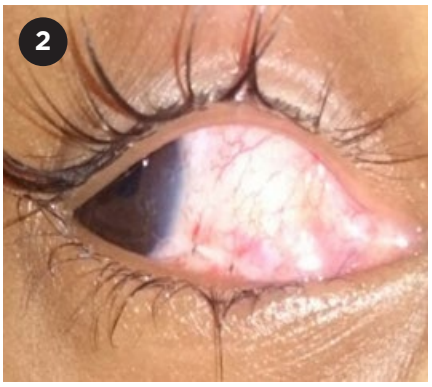
Conservative management. Medical treatment for symptomatic children with small pterygia includes use of artificial tears and weak topical steroids to reduce inflammation and improve comfort.

The child may be advised to wear sunglasses while outdoors; reducing ultraviolet light exposure may decrease the growth stimulus.

Surgery. Surgical therapy may be appropriate for larger pterygia encroaching on the limbus and progressing toward the visual axis.

Indications for surgery include the following:

- Intractable irritation
- Opacity in the visual axis



AFTER TREATMENT. *Rotational conjunctival autograft was used after excision of pterygium.*

- Astigmatism leading to visual impairment
- Cosmetic concerns

Primary pterygium. In children with a primary pterygium, conjunctival autograft is the treatment of choice.[5] Conjunctival rotational autograft (Fig. 2) can be considered, with the caveat that in some active children, constant eye movement may displace the graft.

Recurrent pterygium. In cases of recurrence, a conjunctival autograft technique may be attempted again. As an alternative, we have had good results with the older technique of conventional bare sclera pterygium excision. It is important to note that this surgery must be performed with use of adjunctive therapies, such as mitomycin C, to reduce the otherwise unacceptable risk of recurrence. However, antifibrotic agents are associated with complications, including corneal melting, corneal perforation, prolonged punctate keratopathy, scleral necrosis, secondary glaucoma, and cataract.

Another option is amniotic membrane transplantation, but it is costly, requires preservation, and is not widely available.

Postsurgical care. In our clinic, we advise the following postsurgical regimen: tobramycin sulfate 0.3% drops 6 times per day for 15 days; 1% prednisolone acetate drops 4 times per day for a week, then tapered over 3 weeks; and 0.5% carboxymethylcellulose sodium drops 6 times a day for a month.

For pain, oral nonsteroidal anti-inflammatory drugs are given in pediatric doses according to body weight.

We also instruct the patient not to rub the eye and not to move the eyes excessively.

Follow-up

In our experience, recurrence is more aggressive and occurs earlier—at 4 to 6 months—in children than in adults. Children who have had pterygium excision should be examined every month for 6 months and, subsequently, once every 6 months. Long-term follow-up may yield better understanding of childhood pterygium and its outcome.

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Susan Dsouza, MBBS, DOMS

Two for the Price of One

How did a simple trip to the optometrist for a contact lens fitting turn into an eye-opening experience? For 57-year-old Doris Daisy*—a Floridian, born and bred—the discovery of 2 corneal lesions prompted an initial referral from her optometrist to a cornea specialist and subsequently to our office.

We Meet the Patient

"Raised in the Sunshine State, I've lived in the sun all my life," said Ms. Daisy. She had also traveled to other sunny areas, including Africa. In response to our questions, she reported no blurry vision, no photophobia, and no excess tearing. "A little morning redness is all I can think of—no pain, no irritation, nothing," she recalled.

Ocular history. Ms. Daisy's ocular history was significant for bilateral LASIK surgery 10 years earlier, which was successful, with no complications.

Medical history. She reported no chronic medical conditions and had no history of diabetes, hypertension, infectious disease (including HIV), or cancer. She had never smoked, and she drank alcohol occasionally.

The only abnormality she reported was an abnormal Pap smear.

What We Found

On examination, her best-corrected visual acuity was $20/20^{-1}$ in the right eye and $20/25^{-1}$ in the left eye. Her intraocular pressure was 10 mm Hg bilaterally. Her pupils, confrontation visual fields, and ocular movements were normal. The external exam was unremarkable. No cervical lymph nodes were palpated.

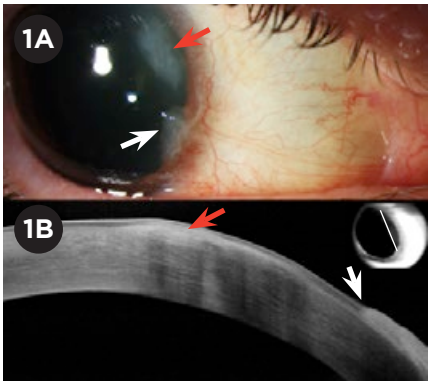
At the slit lamp. The slit-lamp exam of the right eye was notable for 2 lesions (Fig. 1A). The first was a diffuse white nodular lesion occupying the peripheral cornea at 2 to 3 o'clock, with resultant corneal opacification. The second lesion, which extended from the limbus at 3 to 5 o'clock, appeared gelatinous and leukoplakic, with slight neovascularization. Notably, this lesion stained positive with rose bengal. The conjunctiva and cornea of the left eye were normal.

All other anterior chamber and posterior pole findings were unremarkable bilaterally.

Differential Diagnosis

Ms. Daisy presented with 2 lesions, having similar yet distinct characteristics. When forming our differential diagnosis, we needed to consider whether these lesions represented the same or different entities.

Salzmann nodular degeneration. The first lesion we looked at, the upper lesion, presented a classic clinical picture of Salzmann nodular degeneration: an asymptomatic, avascular, white subepithelial nodule in a middle-aged woman. Although the condition is usually idiopathic, chronic irritation and/or a history of ocular surgery—such as Ms. Daisy's LASIK—may predispose a patient to Salzmann nodular degeneration. However, this diagnosis alone failed to characterize the second lesion.



WE GET A LOOK. *(1A) Slit-lamp photo of the right eye demonstrates 2 nasal lesions in the cornea. Although the lesions are similar, there are subtle differences between them: a diffuse, opalescent lesion extends from 2 to 3 o'clock (red arrow), and a gelatinous limbal lesion extends into the cornea from 3 to 5 o'clock (white arrow). (1B) The same 2 lesions as seen on HR-OCT: one has a thin, dark epithelium with underlying hyperreflectivity (red arrow), and the other has a thickened, hyperreflective epithelium and an abrupt transition from normal to abnormal epithelium (white arrow).*

Ocular surface squamous neoplasia (OSSN). The second lesion appeared gelatinous and leukoplakic, with neovascularization, and it stained positive with rose bengal. Although Salzmann nodular degeneration may present as multiple lesions, the characteristics of

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Carol L. Karp, MD

this second lesion were different from the upper one and were highly suggestive of OSSN.

Ms. Daisy had several risk factors we look for in patients with a corneal or conjunctival lesion suspicious for neoplasia: a history of a positive Pap smear, a history of chronic sun exposure, residence at a low latitude, and advancing age.

Pterygium. OSSN and pterygium share many risk factors, including extensive sun exposure and a positive Pap smear, both of which were reported by Ms. Daisy. Pterygium and OSSN can be present concomitantly.

Narrowing the possibilities. At this point, our differential included Salzmann nodular degeneration, OSSN, and pterygium. We ordered high-resolution optical coherence tomography (HR-OCT) to hone in on the diagnosis.

Making the Diagnosis

HR-OCT findings revealed 2 separate lesions with distinct characteristics (Fig. 1B):

- Lesion 1: thin, dark epithelium with subepithelial hyperreflective nodule. These features are consistent with Salzmann nodular degeneration.
- Lesion 2: thickened, hyperreflective epithelium with an abrupt transition from normal to abnormal epithelium. These features are consistent with OSSN. This was not a benign pterygium.

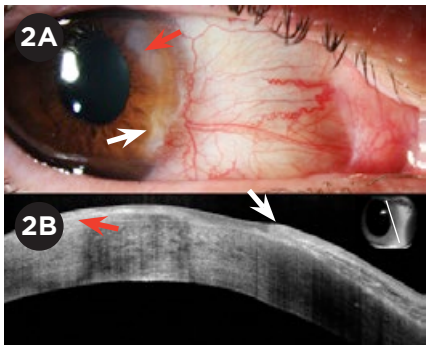
Definitive diagnosis. We determined that a diagnosis of Salzmann nodular degeneration with concomitant OSSN best fit Ms. Daisy's clinical picture.

Discussion

A physician's ability to solve clinical problems decisively and accurately is guided largely by clinical acumen, yet sometimes technology provides vital assistance.

Imaging modalities such as HR-OCT are important adjunctive tools to aid physicians in the diagnosis and management of ocular surface lesions.[1] In this case, HR-OCT allowed us to accurately identify and compare 2 distinct ocular pathologies: Salzmann nodular degeneration and OSSN, both of which were present in the same patient.

Salzmann nodular degeneration. This condition is typically seen in women aged 50 to 60 years old and is characterized by the appearance of diffuse, whitish gray subepithelial nodules. Most cases are bilateral and generally asymptomatic, unless they are visually significant. On HR-OCT, Salzmann nodules appear as hyperreflective subepithelial tissue underlying a thin band of dark, normal epithelium. They are often rounded and dome shaped.[1]



DURING TREATMENT. *(2A) After 2 cycles of 5-FU, opalescent lesion at 2 to 3 o'clock remains unchanged (red arrow), but the size of the gelatinous limbal lesion at 3 to 5 o'clock has been reduced, though neovascularization is prominent (white arrow). (2B) HR-OCT reveals subepithelial hyperreflectivity, with an overlying thin and dark epithelium, classic of Salzmann nodular degeneration (red arrow). The lesion from 3 to 5 o'clock still has an abrupt transition from hyporeflectivity to hyperreflectivity, consistent with OSSN. The thickening of the epithelium is noticeably improved after 2 cycles of 5-FU (white arrow).*

OSSN. In contrast, the clinical appearance of OSSN may be gelatinous, leukoplakic, or papilliform, with prominent neovascularization. Rose bengal may reveal diffuse punctate staining.

Though biopsy remains the gold standard for diagnosis, HR-OCT can be used as a noninvasive adjunctive diagnostic tool for OSSN. On this imaging technique, OSSN appears as thickened, hyperreflective epithelium with an abrupt transition from normal to abnormal epithelium.[1]

Pterygium. Clinically, pterygia are fibrovascular lesions that sometimes mimic OSSN. The transition between normal and abnormal epithelium is as abrupt as that seen in OSSN.

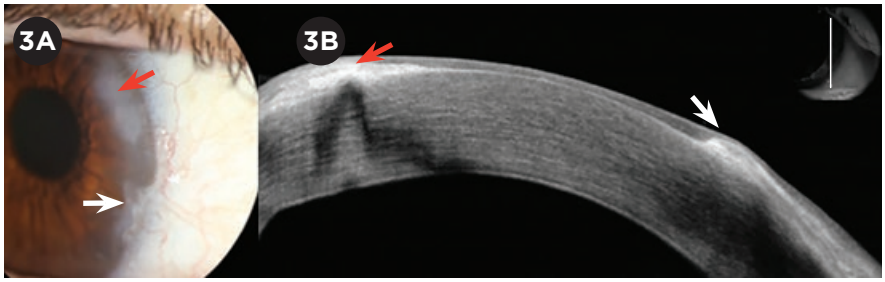
However, unlike OSSN, pterygium demonstrates nonthickened, mildly hyperreflective epithelium overlying a hyperreflective "stringy" subepithelial lesion on HR-OCT.

The key distinction is that pterygium is a subepithelial lesion, while OSSN is epithelial. Both pterygium and OSSN share UV light as a risk factor. Because pterygia sometimes precede the development of OSSN, the clinician should remain vigilant for signs of neoplastic disease.

Treatment

With the emergence of HR-OCT in the diagnosis of various ocular surface diseases, topical chemotherapy has become the preferred treatment for OSSN. Topical mitomycin C, 5-fluorouracil (5-FU), and interferon alfa-2b are all effective chemotherapeutic agents in the treatment of OSSN.[2]

Our patient elected to receive 5-FU, cycled 1 week on/3 weeks off. Cycling



RESOLUTION. *(3A) After 4 cycles of 5-FU, the upper lesion (red arrow) is unaffected, and the previously noted gelatinous lesion has resolved (white arrow). A small pterygium is now visible in the area of the resolved OSSN. (3B) HR-OCT shows a classic Salzmann subepithelial lesion (red arrow), while the other lesion has resolved. Only subepithelial scarring/hyperreflectivity is noted, which is consistent with an underlying pterygium (white arrow).*

Carol L. Karp, MD

helps diminish the irritating effects of 5-FU. Our patient completed 4 weekly cycles of 5-FU.

Continuing follow-up. Ms. Daisy received 1 final cycle of 5-FU, and she will be followed carefully.

Imaging after treatment. Slit-lamp photos and HR-OCT images were obtained after 2 cycles (Figs. 2A, 2B) and 4 cycles (Figs. 3A, 3B). As anticipated, the Salzmann nodular degeneration remained unaffected by the chemotherapeutic agent, while the OSSN lesion demonstrated marked clinical improvement.

And there's more. Interestingly, once the OSSN lesion had resolved, a small pterygium head was visible at the origin of the cancerous lesion. Sunlight is a risk factor for both pterygium and OSSN, and careful monitoring of all pterygia for evidence of neoplastic disease is wise.

Final Thoughts

Role of HR-OCT. Ms. Daisy's case demonstrates the value of HR-OCT in the management of ocular surface conditions. This imaging modality enabled us to establish the 2 separate diagnoses without biopsy. Further, it revealed complete clinical response and normalization of the epithelial hyperreflectivity and thickening, confirming the full resolution of the OSSN lesion with the topical 5-FU treatment.

Be vigilant. This is not the first,[3] nor will it be the last, case of concomitant Salzmann nodular degeneration and OSSN. Therefore, it is important for clinicians to recognize that both lesions may be present in the same patient, and even in the same eye.

* Patient name is fictitious.

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Mr. Diel is a medical student at the Miller School of Medicine at the University of Miami. **Dr. Mercado** is research fellow, and **Dr. Karp** is professor of ophthalmology and Richard K. Forster Chair in Ophthalmology; both are at the Bascom Palmer Eye Institute in Miami. *Relevant financial disclosures: None.*

3 Subspecialties, 4 Experts, and the Next 5 Years

A look into the future of cornea, oculoplastics, and retina.

By Evan H. Black, MD, FACS, Lawrence Halperin, MD, Christopher J. Rapuano, MD, and Kathryn P. Winkler, MD

AS 2017 WRAPS UP, EYENET APPROACHED SEVERAL OF ITS editorial board members, asking them to identify a news item or trend from this year that could significantly shape their subspecialty or all of ophthalmology over the near term, say, the next 5 years. These experts—Christopher J. Rapuano, MD, cornea; Evan H. Black, MD, oculoplastics, and his colleague Kathryn P. Winkler, MD; and Lawrence S. Halperin, MD, retina—approached the project with their own style, perspective, and thought process. The write-ups are as personal and unique as each of the authors and will help readers move into 2018 and beyond.

DR. RAPUANO ON CORNEA

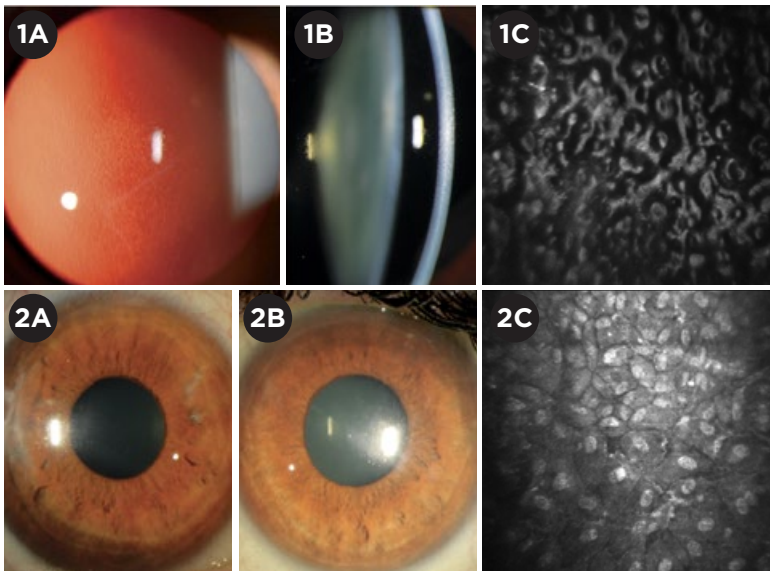
Corneal Endothelial Cell Regeneration Therapy: The Way of the Future?

Endothelial cell dysfunction is a leading cause of corneal transplantation around the world. In fact, corneal edema due to endothelial cell failure has been the No. 1 indication for transplantation in the United States for many years.[1] Penetrating keratoplasty (PK) was the procedure of choice for these eyes until the early 2000s, when endothelial keratoplasty (EK) was introduced. EK yields faster visual recovery, less change in refractive error, less irregular astigmatism, and a much smaller wound, resulting in lower risk of a wound dehiscence. EK overtook PK as the primary corneal transplant procedure performed in the United States for all indications in 2012.[1]

However, EK isn't perfect. It requires highly trained surgeons, an operating room infrastructure, and follow-up by appropriately trained physicians to manage complications such as graft rejection and glaucoma. It also requires adequate

donor material and a functioning eye banking system. All of these components are rather costly, limiting the use of EK worldwide.

These limitations to corneal transplant surgery have led to investigations into alternative treatments for endothelial cell dysfunction, including simply removing the central unhealthy endothelial cells, thus allowing peripheral endothelial cells to migrate and cover the central cornea; using medications to stimulate healthy endothelial cell proliferation; and transplanting donor endothelial cells or, even better, the patient's own endothelial cells (potentially derived from their own stem cells). While none of these therapies is "ready for prime time" yet, I believe over the next 5 years, we will be treating corneal endothelial cell dysfunction differently from today.



DISCOVERY. *In 2012, Shah, Randleman, and Grossniklaus reported a patient with polymorphous membrane dystrophy who underwent DSEK, which failed.[2] Yet the patient demonstrated spontaneous corneal clearing (1A, 1B, right eye before; 2A right eye, 2B left eye after) and endothelial cell repopulation of right eye (1C before, 2C after).*

Primary Descemetorhexis

The first time I heard of the concept of simply removing the central unhealthy endothelium and Descemet membrane was when Brad Randleman gave a case presentation regarding a young woman with Fuchs dystrophy/posterior polymorphous corneal dystrophy who underwent Descemet stripping EK (DSEK). The DSEK graft completely detached, but the cornea still cleared, so the detached graft was removed. He later published this case.[2] In the article, he included follow-up: The first eye remained clear, and he subsequently performed primary descemetorhexis surgery in the fellow eye, which also cleared, with central endothelial cell repopulation in both eyes. At the time, the hypothesis was that the peripheral endothelial cells were simply migrating centrally to cover the denuded area, as corneal endothelial cells were thought not to proliferate.

There have been several publications on this technique with mixed results.

Poor results. Arbelaez et al.[3] had poor results in 3 eyes undergoing 6.0-6.5 mm diameter descemetorhexis for Fuchs dystrophy. Additionally, they found poor adherence of subsequent Descemet membrane EK (DMEK) in the eye that underwent that procedure. Koenig[4] had poor results with a 6-mm diameter descemetorhexis in 2 eyes with Fuchs dystrophy at the time of cataract surgery.

Good results. On the other hand, Borkar et al.[5] performed a 4-mm diameter descemetorhexis in 13 eyes of 11 patients with Fuchs dystrophy at the time of cataract surgery. Four corneas cleared by 1 month (termed "fast responder"), 4 additional corneas cleared by 3 months ("responder"), and 2 more corneas cleared by 6 months ("slow responder"). Three corneas did not clear, and all 3 underwent successful DMEK with no need to rebubble.[6]

Mixed results. Iovieno et al.[7] found unpredictable results using a 4-mm central descemetorhexis in 5 patients.

The downside to this approach is that most surgeons believe that the actual number of functioning endothelial cells isn't increased and, therefore, the total endothelial cell density decreases.

Enhancing Corneal Endothelial Cell Proliferation and/or Function

While human corneal endothelial cells are not thought to multiply naturally after birth, one approach is to use "growth factors" to induce the healthy endothelial cells to proliferate (increasing their absolute number). The most studied of these growth factors are the rho kinase inhibitors. In animal models and small human studies, rho kinase inhibitors have been demonstrated to slow progression of endothelial cell degeneration and also restore normal endothelial cell counts after endothelial cell injury.[8-13] Needless to say, uninhibited growth of cells in the anterior chamber has potential side effects, including covering the

trabecular meshwork and inducing glaucoma.

Using a combination of surgical removal of unhealthy central corneal endothelial cells and a topical rho kinase inhibitor, ripasudil, to improve corneal endothelial cell function, Moloney et al.[14] performed a 4-mm diameter descemetorhexis in 12 eyes of 11 patients with Fuchs dystrophy. Nine of the 12 corneas cleared between 2 and 5 months postoperatively. In the other 3 eyes, topical ripasudil was applied to aid in repopulation, and 2 of these 3 corneas cleared.

Corneal Endothelial Cell Replacement Therapies

While corneal transplantation replaces endothelial cells, there is great interest in both simplifying the technique of transferring these cells and potentially using cells from the patients themselves, thereby avoiding the need for donors. There are several potential sources for endothelial cells, including embryonic stem cells; the patient's own stem cells, including adult stem cells (progenitor cells) and induced pleuripotent stem cells; and donor corneal endothelial cells expanded in vitro.

Embryonic stem cells have issues with immune rejection and tumorigenicity as well as ethical concerns regarding the use of human embryos. Induced pleuripotent stem cells have great potential, but they may not be as "pleuripotent" as originally hoped. Adult stem cells/progenitor cells for the corneal endothelium have been found in the corneal limbus. While not as pleuripotent as embryonic stem cells or induced pleuripotent stem cells, they may be suitable for endothelial cell transplantation. Adult human skin cells have also been successfully induced to produce "corneal endothelial-like cells."[15]

Expanding donor endothelial cells in vitro eliminates the problems of getting stem cells to differentiate into corneal endothelial cells, but it obviously involves getting these cells to proliferate, which has been problematic. One important advantage to this technique is the potential ability to treat multiple patients with a single donor cornea.

No matter which cells are being used to repopulate the corneal endothelium, the optimal delivery method is still up for debate. Cells can be injected and the patient placed in a prone position allowing gravity to pull the cells toward the posterior cornea. Tiny magnetic particles and nanoparticles have also been used to position endothelial cells.[16,17] Additionally, a variety of artificial corneal scaffolds have been used, but those techniques involve potentially complicated corneal surgical procedures.

Conclusion

Current corneal transplant techniques, while quite successful, are labor and cost intensive. A variety of evolving therapies have the potential to change the manner in which we treat corneal endothelial abnormalities over the next 5 years.

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DR. BLACK AND DR. WINKLER ON OCULOPLASTICS

Beyond Blepharoplasty: Lifting the Forehead

With the wealth of information available to patients, who have become more educated about aesthetic surgery, the demand for minimally invasive and highly efficacious forehead lifting procedures continues to grow. Newer endoscopic forehead lifting techniques allow for faster recovery, less pain, and fewer risks and complications while providing better, longer-lasting results. Over the coming years, surgeons who perform blepharoplasty will need to be equipped with an understanding of the eyebrow and forehead anatomy and the role these have in the appearance of the aging face.

Often when a patient presents with complaints of drooping upper eyelids or excess upper eyelid skin, he or she has a combination of blepharoptosis and/or dermatochalasis and brow ptosis. Descent of the brow, subbrow fat pad, and forehead contributes to an appearance of fatigue or anger, which interferes with the patient's nonverbal communication. Patients are mostly unaware of changes in the brow position and attribute their tired appearance to excess upper eyelid skin

alone. It is therefore imperative to accurately evaluate and communicate the clinical findings with the patient.

Exam Basics

A patient who presents with complaints of upper eyelid crowding should have a thorough clinical evaluation, with particular consideration of the margin to reflex distance 1 (MRD1), presence of dermatochalasis, and presence and severity of brow ptosis. Upper eyelid skin descending over the lateral lashes (Connell's sign) is classic for brow ptosis. The presence of deep forehead rhytids can be an indication of prolonged frontalis engagement. The true degree of brow ptosis is best measured by manually fixating the brow while the patient closes his or her eyes, then asking the patient to gently open the eyes.

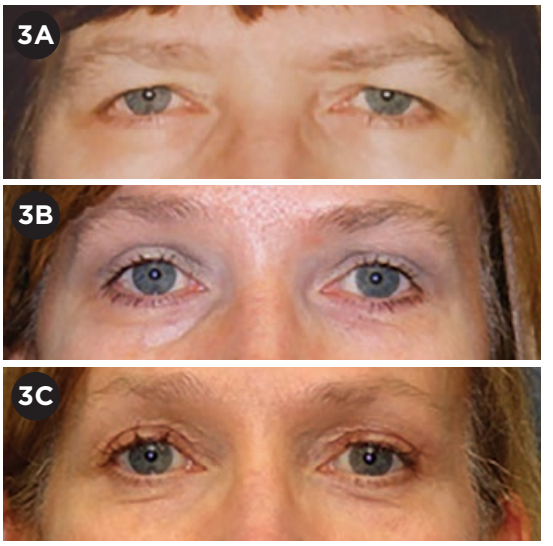
The positioning of the eyebrow is affected by such factors as brow elevator and depressor muscles, genetics, gravity, skin laxity, surgery, trauma, and the patient's expressivity. In general, the female eyebrow should lie approximately at or above the superior orbital rim. It should have a curve with the tail of the brow higher than the head of the brow. The male eyebrow should be at the level of the superior orbital rim with a less arched configuration. Presence of supraplaced brow tattoo or makeup is important to note as well.

A patient with complaints consisting mostly of visual disturbance in the superior half of the visual field may only be interested in pursuing a blepharoptosis repair or functional blepharoplasty. Those patients interested in achieving facial rejuvenation with a more aesthetic emphasis should be considered for a forehead lifting procedure alone or with a blepharoptosis repair or blepharoplasty. Providing the patient with a handheld mirror during the examination can help with demonstrating the patient's anatomy and goals of each surgery. Preoperative photos should be obtained, including flashed and unflashed photos, side views, and three-quarter views.

Surgical Options

There are a number of surgical options for lifting the brow, each with varying indications and advantages.

A direct brow lift is achieved by excising an ellipse of suprabrow tissue. This surgical procedure may be considered when the patient has a visual function disturbance that cannot be corrected through upper eyelid surgery alone due to significant and severe brow ptosis. Given the inevitable scarring caused by this intervention, this procedure should not be considered for patients who want a cosmetic outcome. This procedure may be covered by insurance if there is interference with activities of daily living due to the visual obstruction.



BEFORE AND AFTER. *A patient of Dr. Black's (3A) before, (3B) shortly after, and (3C) 6 years after an endoscopic forehead lift.*

A midforehead lift, similarly, is performed by removing an ellipse of tissue across the entire forehead, placing the incision in a deep forehead rhytid. Again, this procedure should not be considered for a cosmetically motivated patient.

A transblepharoplasty brow lift is performed at the time of upper eyelid surgery. A dissection is carried up through the lid crease incision, and the brow is fixated to the superior lateral orbital rim. This achieves a mild temporal lift. For reimbursement purposes, this procedure may be considered "bundled" with functional upper eyelid surgery.

Cosmetic procedures. The pretrichial, coronal, and endoscopic foreheadplasty procedures are all options for the cosmetic brow lift patient.

A pretrichial lift is best performed in a patient with a high forehead as it will shorten the forehead, thus lowering the hairline. It is performed through an incision just anterior to the hairline with a dissection in the subgaleal plane.

A coronal forehead lift requires an incision at the coronal suture, extending from ear to ear. Similar to a pretrichilal lift, the forehead lift is performed in a subgaleal plane.

The endoscopic forehead lift is a minimally invasive procedure to lift the brow, performed in the avascular subperiosteal plane. In general, this procedure results in minimal to no scarring with lasting results.

Performing the Endoscopic Lift

The endoscopic forehead lift will allow for elevation of the brow and subbrow fat pad, as well as reduction of forehead and glabellar rhytids, and

Evan H. Black, MD, FACS

improvement of lateral canthal hooding.

Our endoscopic forehead lift technique places all incisions behind the hairline, without the need to shave the hair. Surgical sites are marked with 2 temporal elliptical incisions in all cases, 2 paracentral incisions for men, and 1 central plus 2 paracentral incisions for women. The supraorbital notch should be identified, and a "safety zone" 2 cm around the notch should be drawn.

After thorough local anesthetic is administered, the temporal ellipses are excised, and a dissection is carried out to the deep temporalis fascia. In this plane the facial nerve is superior to the dissection, which prevents injury. The endoscope is used to visualize the temporal dissection down to the lateral canthal angle. Once the zygomaticoemtemporal (or sentinel) vein is encountered the dissection is complete.

Next, the central and paracentral incisions are created down to the periosteum. A blind subperiosteal dissection is carried out, avoiding the areas of the supraorbital "safety zone" markings. Once complete, the endoscope is again used to visualize the supraorbital bundle to allow for complete dissection around these important structures. The temporal and central dissection pockets are then connected by releasing the conjoint tendon.

Once released, 2 holes are drilled into the outer calvarium just anterior to the hairline in the area of maximal desired arch of the brow. Endotine (MicroAire) anchors are placed in these drill holes and the forehead is fixed to the Endotines. The superficial temporalis fascia is sutured and the skin incisions are closed using staples.

Conclusion

Being familiar with the various brow lifting procedures is important for any surgeon who evaluates and operates on patients who present with upper eyelid crowding or drooping complaints. This familiarity allows the patient and surgeon to discuss and determine the most appropriate surgical intervention for any patient depending on the patient's goals of surgery. Utilizing modern endoscopic techniques, surgeons and their patients can expect to have excellent, long-lasting results along with faster recovery and fewer complications.

DR. HALPERIN ON RETINA

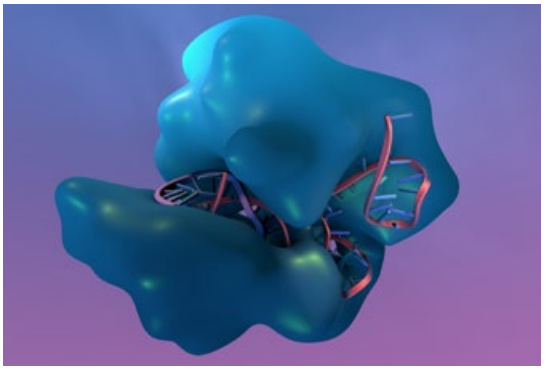
The Future is Now???

Retina has come a long way in the past 15-25 years. Surgical success rates are improving, complications are diminishing, surgical time is dropping. Gone are the days of watching macular disease steal vision from the ever-increasing number of aging or diabetic patients. The era of anti–vascular endothelial growth factor (VEGF) drugs has created nothing short of a sea change in our treatment. Yet, there is still much to do. Here is a list of what I hope is achievable in the next 5-10 years:

Exudative age-related macular degeneration (AMD). Anti-VEGF treatment is outstanding at preventing vision loss but mediocre at improving lost vision. New treatments for vision improvement have been elusive, but I am still hopeful.

Anti-VEGF drugs reliably reduce or eliminate leakage. However, atrophy and/or fibrosis eventually develop in a high percentage of patients. Future treatments to reduce or eliminate these damaging developments should improve vision outcomes. We thought Fovista would be the first-in-class antifibrotic, but the clinical trial did not deliver.

Dry AMD. A treatment for geographic atrophy (GA) is in development at Genentech and other locations. This treatment, too, may prevent further visual and functional loss, but it will not restore lost vision. Now, marginal data is threatening to derail this first-in-class treatment. Whether restoration of some sight is achievable with stem cell therapy, genetic manipulation, or some other method is still unknown, but researchers are actively investigating. Preventing vision loss in GA would be a major step forward, as this condition seems to be increasingly prevalent.



CRISPR. *The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene-editing system is opening the door to medical discovery.*

Injections. As the indications for intravitreal drugs expand, the number of these procedures performed by retina surgeons will grow, even if the long-acting delivery device currently under investigation by Genentech is successfully developed. Preloaded syringes from Genentech have already received positive reviews, and I suspect

the concept will spread among manufacturers.

Retinal degenerations and genetics. Teams of molecular biologists spent a decade and $1B sequencing the genome of a single human being not that long ago. Now, this can be done in a short time for a few thousand dollars. Clearly this trend will continue, and as it applies to retinal disease, we will be able to identify all gene-related retinal disease more quickly, accurately, and inexpensively than ever before.

As we find disease-causing genes, the ability to make the leap from gene identification to treatment remains mostly elusive. The biggest development in molecular genetics therapy is CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), the most efficient and approachable gene-editing system ever invented. Our ability to control this environment will become the central issue in the future of medical discovery and treatment.

Surgical retina. Improvements in vitrectomy, from instrumentation to comfort of surgery to results, have been impressive in the past 15 years. However, there is more to accomplish. Specifically, proliferative vitreoretinopathy (PVR) remains an infrequent but important cause of failure of retinal detachment surgery. Medications such as methotrexate have been suggested but not proven to prevent PVR. This could be a perfect target for CRISPR.

Small-gauge vitrectomy has changed the way we approach retinal diseases as well as the patient experience. Gone are the days of postop pain, eye swollen shut, high intraocular pressure, and very slow vision recovery. A vitrectomy/sclera buckle for retinal detachment can be achieved in under an hour. Almost gone are the days of extensive facedown positioning, as many surgeons realize that it does not contribute to improved outcomes.

Diabetic retinopathy (DR). Laser and anti-VEGF therapy are the mainstays of treatment and have clearly reduced the incidence of severe vision loss. As anti-VEGF injections continue to demonstrate a benefit in prevention and treatment of diabetic macular edema and proliferative DR, retina specialists have reached a very high level of effectiveness.

Early identification remains an important problem. For myriad reasons, many diabetic patients do not come in for eye exams at the early stages of disease. Despite advances ranging from nonmydriatic cameras to artificial intelligence–driven photographic interpretation, diabetics are still required to sit in front of a camera. Until drones can fly around and take photos of retinas without permission, I'm not sure how we are going to move the needle on this common and preventable cause of vision loss.

And, despite incredible advances in anti-VEGF treatment and surgical approaches for DR, a treatment for retinal ischemia remains elusive. I hope the next 10 years brings us a treatment to prevent, or even reverse, capillary closure and retinal ischemia in our patients with diabetes.

Conclusion. Retina is at the forefront of advances in medicine. Technologic improvements in the operating room, scientific improvements in biologics, and genetic understanding of disease have contributed to our ability to help patients maintain, improve, and preserve their sight.

This has all come at a high financial cost, and as the health care system bends under the weight, we as physicians will be challenged to provide cutting-edge care in the most efficient and affordable way. We hope to continue to provide the very best care to every patient.

MEET THE EXPERTS

Christopher J. Rapuano, MD Director of the cornea service and co-director of the refractive surgery department at Wills Eye Hospital and professor of ophthalmology at Jefferson Medical College, both in Philadelphia. *Relevant financial disclosures: None.*

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Lawrence S. Halperin, MD Retina specialist at the Retina Group of Florida in Boca Raton. *Relevant financial disclosures: Regeneron: C.*

Kathryn P. Winkler, MD Oculoplastic surgeon at Consultants in Ophthalmic & Facial Plastic Surgery in Southfield, Mich. *Relevant financial disclosures: None.*

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Scribes, Techs, and Orthoptists

Tests. Well-trained, scribes, techs, and orthoptists can perform tests with a technical (–TC) component, provided that these steps are taken.

- The physician evaluates the patient and determines what tests are necessary.
- An order is written that includes the type of test and which eye(s) should undergo testing. With a verbal order from the physician, staff may document the physician's delegated order.
- The medical record reflects the medical necessity for the tests.
- The physician promptly provides the interpretation of the test.

E&M services. Techs and orthoptists may perform one level of established patient exam following a physician order that details what elements of the exam are medically necessary. The technician code (CPT code 99211) has this description: *Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician or other qualified health care professional. Usually the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.* To learn more, read "When Techs See Patients" (Savvy Coder, October 2007).

Since April 2003, the National Correct Coding Initiative (CCI) has bundled all tests with exam level 99211.

Signature. Because billing is under the ordering physician's National Provider Indicator (NPI), the physician must be on site and sign the exam note.

Earlier this year, CMS updated its guidance on signature requirements. *CMS Transmittal 713* described the new policy, which came into effect on June 6, 2017, as follows: "Scribes [and technicians and orthoptists] are not providers of items or services. When a scribe is used by a provider in documenting medical record entries (e.g., progress

MIPS—Jan. 15 Deadline for IRIS Registry Users

MIPS reporting. The IRIS Registry is a one-stop shop for the Merit-Based Incentive Payment System (MIPS). Use it to report MIPS' quality measures, advancing care information (ACI) measures, and improvement activities.

Finish entering your MIPS information into the IRIS Registry web portal by Jan. 15, 2018. This deadline applies to ACI attestation, improvement activities attestation, and—if you haven't integrated your electronic health record (EHR) system with the IRIS Registry—reporting of quality measures. If you have integrated your EHR system with the IRIS Registry, your MIPS quality data is automatically extracted from your EHRs, but ACI measures and improvement activities must be reported manually.

Submit a signed data-release consent form for each provider by Jan. 15, 2018. The IRIS Registry won't submit a provider's MIPS data to the Centers for Medicare & Medicaid Services (CMS) unless it has received the signed consent form by Jan. 15. You must submit a new consent form each year. Starting in early December, you can submit consent forms via the IRIS Registry dashboard. For instructions, see aao.org/consent-form.

What if you aren't participating in the IRIS Registry? If you missed the deadline to sign up for the IRIS Registry, you have several other MIPS reporting options. For more information, read "MIPS—Today's To-Do List: Avoid the Payment Penalty" (Savvy Coder, November 2017).

Learn more. See aao.org/iris-registry and aao.org/medicare.

BY **SUE VICCHRILLI, COT, OCS,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT, **CHERIE MCNETT,** DIRECTOR OF HEALTH POLICY, **MICHAEL X. REPKA, MD, MBA,** MEDICAL DIRECTOR OF HEALTH POLICY, AND **GEORGE A. WILLIAMS, MD,** SECRETARY FOR FEDERAL AFFAIRS.

notes), CMS does not require the scribe to sign/date the documentation. The treating physician's/NPP's signature on a note indicates that the physician/NPP affirms the note adequately documents the care provided. Reviewers are only required to look for the signature (and date) of the treating physician/NPP on the note. Reviewers shall not deny claims for items or services because a scribe has not signed/dated a note."

While physicians are required to provide an attestation statement, CMS doesn't instruct physicians to use a specific form or format for that attestation, but the agency indicates that the following example is acceptable: "I, [print full name of the physician/practitioner], hereby attest that the medical record entry for [date of service] accurately reflects signatures/notations that I made in my capacity as [insert provider credentials, e.g., M.D.] when I treated/diagnosed the above listed Medicare beneficiary. I do hereby attest that this information is true, accurate, and complete to the best of my knowledge and I understand that any falsification, omission, or concealment of material fact may subject me to administrative, civil, or criminal liability."

Physician Assistants (PA) and Nurse Practitioners (NP)

Licensing. PAs and NPs are licensed, and they must maintain education credits as their state licensure requires. Like physicians, they must enroll—and re-enroll every 3 to 5 years—in Medicare and with commercial insurances.

Billing and NPIs. PAs and NPs can bill services for established patients under their own National Provider Identifier (NPI); in this instance, payment would typically be 85% of the physician allowable. Alternatively, they can bill under the physician's NPI with the full fee schedule allowable. *CMS Transmittal 178* specifies that the service provided must be medically necessary and the service must be within the scope of practice for an NPP in the state in which he or she practices.

The H&P exam. In 2009, when CMS mandated that a history and physical (H&P) exam be performed on every patient undergoing a surgical procedure, some high surgical volume practices hired a PA or NP to perform this service, and claims were submitted independently from the physician's NPI.

PAs and NPs are exempt from the deactivation rule. Good news. According to *MLN Matters SE1034,* PAs and NPs are excluded from the process that would deactivate them for inactivity if they don't submit a claim under their own NPI for 12 months.

Team-Based Care

As team-based care becomes increasingly important in ophthalmology, it is critical to know the relevant rules and regulations regarding NPPs.

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Academy Notebook

NEWS ▫ TIPS ▫ RESOURCES

WHAT'S HAPPENING

New: Ophthalmologists Business Summit

The Academy is launching its first physician-oriented business summit, designed exclusively for Academy members. It takes place March 24-25 in Dallas and will address the key financial and operational challenges your practice is facing right now. The summit was created to address a need consistently raised by members for practice management training to help cope with the evolving practice management environment, especially relating to health care reform, reimbursement issues, electronic health records, and planning for/prospering in the future. Topics include:

- improving profitability by identifying cost-cutting opportunities;
- increasing patient referrals through social media and other marketing tools;
- protecting your practice from cyber threats like ransomware that could cost thousands of dollars;
- leveraging available tools like the Academy's IRIS Registry; and
- incorporating process improvement strategies to build a healthy and sustainable practice.

"Don't miss this rare opportunity to gain valuable insights and exchange knowledge with your peers in an intimate and focused setting," said Ravi D. Goel, MD, Ophthalmologists Business Summit Program Director. "I look forward to seeing you in a couple of months in Texas."

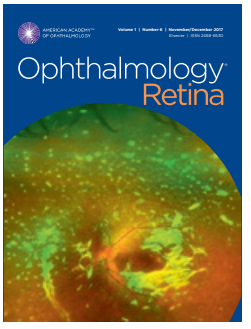
ATTEND THE OPHTHALMOLOGISTS BUSINESS SUMMIT MARCH 24-25 IN DALLAS. *Gain valuable insights and actionable strategies that positively impact practice revenue and growth.*

For details and to register, visit aao.org/business-summit.

Ophthalmology Retina: Now Monthly

The Academy's new retina journal was published bimonthly in 2017. In January 2018, *Ophthalmology Retina* will move to publishing monthly. As always, the journal will continue to feature high-impact articles in the retina field. Academy members receive a discounted rate of $299 for 12 issues.

To subscribe, visit aao.org/store. **To submit a paper,** visit aao.org/retinajournal.



TAKE NOTICE

Need a Holiday Gift Idea? Donate to the Foundation

This is the perfect time of year to make a gift to the Academy Foundation in honor or memory of a mentor, colleague, or family member. Your tax-deductible donation—particularly at the Partners for Sight level ($1,000–$2,499)—will be used to support the Academy programs that are important to you, including the ONE Network, the IRIS Registry, EyeCare America, and more. Be sure to make your gift by Dec. 31 to receive the tax deduction for 2017.

Learn more at aao.org/foundation.

ACADEMY STORE

Get Hands-On Guidance With 2018 *Focal Points*

Each issue of *Focal Points* presents a different clinical topic, providing concise information you can apply to practice immediately. Each issue tackles a specific topic and discusses diagnosis, treatment, and the latest standards of care. Topics for 2018 include Micro-Invasive Glaucoma Surgery and Cataract Surgery Synergy; Masquerades of Age-Related Macular Degeneration; and Optical Coherence Tomography for the Management of Glaucoma. Subscribe to the digital version of *Focal Points* for a new topic every month plus access to the digital archive of more than

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100 topics—all *Focal Points* issues are downloadable, printable, and searchable. Print subscribers get all the benefits of the digital version, plus 12 print issues from January to December of 2018.

To subscribe, visit aao.org/focal-points.

MEETING MATTERS

2018 Abstract Deadlines

To present at AAO 2018, you must submit an abstract online. The abstract submitter for instruction courses and new Skills Transfer labs opens Dec. 14, 2017, and closes Jan. 9, 2018.

To submit, visit aao.org/presenter-central.

AAO 2018 in Chicago

AAO 2018 will take place Oct. 27-30 and will be preceded by Subspecialty Day, Oct. 26-27. Join your colleagues and the Academy at Chicago's McCormick Place for the world's most comprehensive ophthalmic meeting, featuring game-changing research, techniques, and technologies.

For more information, visit aao.org/2018.

Claim CME for AAO 2017

Registrants whose attendance was verified at AAO 2017 and/or Subspecialty Day can claim CME credits online. CME transcripts that include AAO 2017 credits entered at the Academy's annual meeting are available to Academy members at aao.org/cme-central beginning Dec. 7.

For more information, visit aao.org/annual-meeting/cme.

Enjoy Archived Virtual Meeting Sessions

The Virtual Meeting is a free online component of AAO 2017. View 16 archived sessions from New Orleans (approximately 20 hours of educational content) online through Feb. 14, 2018, using your Academy login and password. The 2017 AAO Virtual Meeting is not eligible for CME credit.

For more information, visit aao.org/virtual-meeting.

D.C. REPORT

Academy Monitors Suggested Repeal and Replacement of MIPS

In October, the Medicare Payment Advisory Commission (MedPAC), a congressional Medicare advisory body, suggested that lawmakers scrap the Merit-Based Incentive Payment System (MIPS). The MedPAC commissioners believe that MIPS is an ineffective program with no real ability to drive quality in health care and that it creates too many burdens for most physicians. As an alternative, MedPAC wants to use a 2% penalty to encourage participation in alternative payment models; however, ophthalmology has no alternative payment models. MedPAC is expected to formalize this recommendation when it meets in January, but Congress has no obligation to adopt MedPAC's recommendations.

The Academy's take. While the Academy shares the commission's perspective on the burdens and complexities of MIPS, it remains skeptical of such a monumental change to this federal health program. The Academy has worked hard to preserve a fee-for-service pathway for ophthalmologists and has given the Centers for Medicare & Medicaid Services and Congress a list of changes that would make MIPS a more effective, less burdensome experience for physicians. This list includes giving more credit for participation in the Academy's IRIS Registry, which is uniquely designed to serve as a mechanism for impacting quality of care and patient outcomes.

MIPS is the result of an overwhelming bipartisan effort, making both parties invested in its success. In conversations the Academy has had with leaders in the House of Representatives and Senate, it is clear that Congress wants to give MIPS time to evolve and improve.

MEMBERS AT LARGE

People

The Cornea Society awarded **Khoa D. Tran, PhD,** the 2017 Cornea Society/Richard C. Troutman, MD, DSc (HON) Prize during the Cornea and Eye Banking Forum on Nov. 10. The award includes a $5,000 honorarium from the Troutman Endowment. It is bestowed annually by the society for the paper published in *Cornea* during the previous year that was judged to be most outstanding and innovative and was authored by an investigator 40 years of age or younger. This year's winning paper is titled "Rapid Warming of Donor Corneas Is Safe and Improves Specular Image Quality." Dr. Tran said, "I am excited and honored to have been selected for the Troutman Prize. I would like to take this opportunity to congratulate our team for being recognized for their tireless dedication to restore sight and advance corneal research, and to thank the eye donors and their families for their generous gifts, which make it all possible."

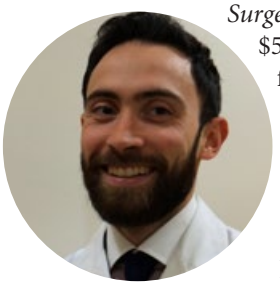
Khoa D. Tran, PhD

Emily Y. Chew, MD, was selected to receive the 2017 Women in Ophthalmology (WIO)/Suzanne Véronneau-Troutman Award. The award was presented to Dr. Chew during AAO 2017 in New Orleans. It recognizes the ophthalmologist who has done the most in the preceding year to promote the role of women in ophthalmology, and it includes a $1,000 honorarium from the Troutman Endowment. Dr. Chew said, "It is indeed a

Emily Y. Chew, MD

great honor to be awarded the Suzanne Véronneau-Troutman Award, as I join a group of stellar women leaders in ophthalmology. Suzanne is a terrific role model and a pioneer in areas where very few women ventured. I love the fact that we are both Canadians whose careers took us to the United States. Suzanne had an incredible career and was a mentor to many. Her vision in promoting women has been extraordinary, and her generosity not only to WIO but also to institutions both in Canada and the United States continues to carry on her legacy. I am very humbled by this award, and I hope we can continue to carry out the mission of nurturing future generations to believe in the power of women."

The International Society of Refractive Surgery (ISRS) awarded **Riccardo Vinciguerra, MD,** the 26th Annual Richard C. Troutman, MD, DSc (HON) Prize during the ISRS Awards ceremony on Nov. 10. This prize recognizes the scientific merit of a young author publishing in the *Journal of Refractive Surgery* and includes a $5,000 honorarium from the Troutman Endowment. Dr. Vinciguerra said, "I am sincerely honored and grateful to have been selected by ISRS and the Academy as the recipient of the 2017 Troutman award, particularly this year when the ophthalmology community mourns the passing of Dr. Troutman—a giant in the field of anterior segment. My father, **Paolo Vinciguerra, MD,** and I had the great pleasure of meeting him personally. I hope that this article will adequately honor his memory. The study, done in collaboration with **Renato Ambrósio Jr., MD, PhD, Cynthia Roberts, PhD, Ahmed Elsheikh, PhD,** and my father, aimed to create a new biomechanical index to separate healthy from keratoconic patients. I hope that the introduction of the Corvis Biomechanical Index in clinical practice will increase the accuracy of ectasia screening."



Riccardo Vinciguerra, MD

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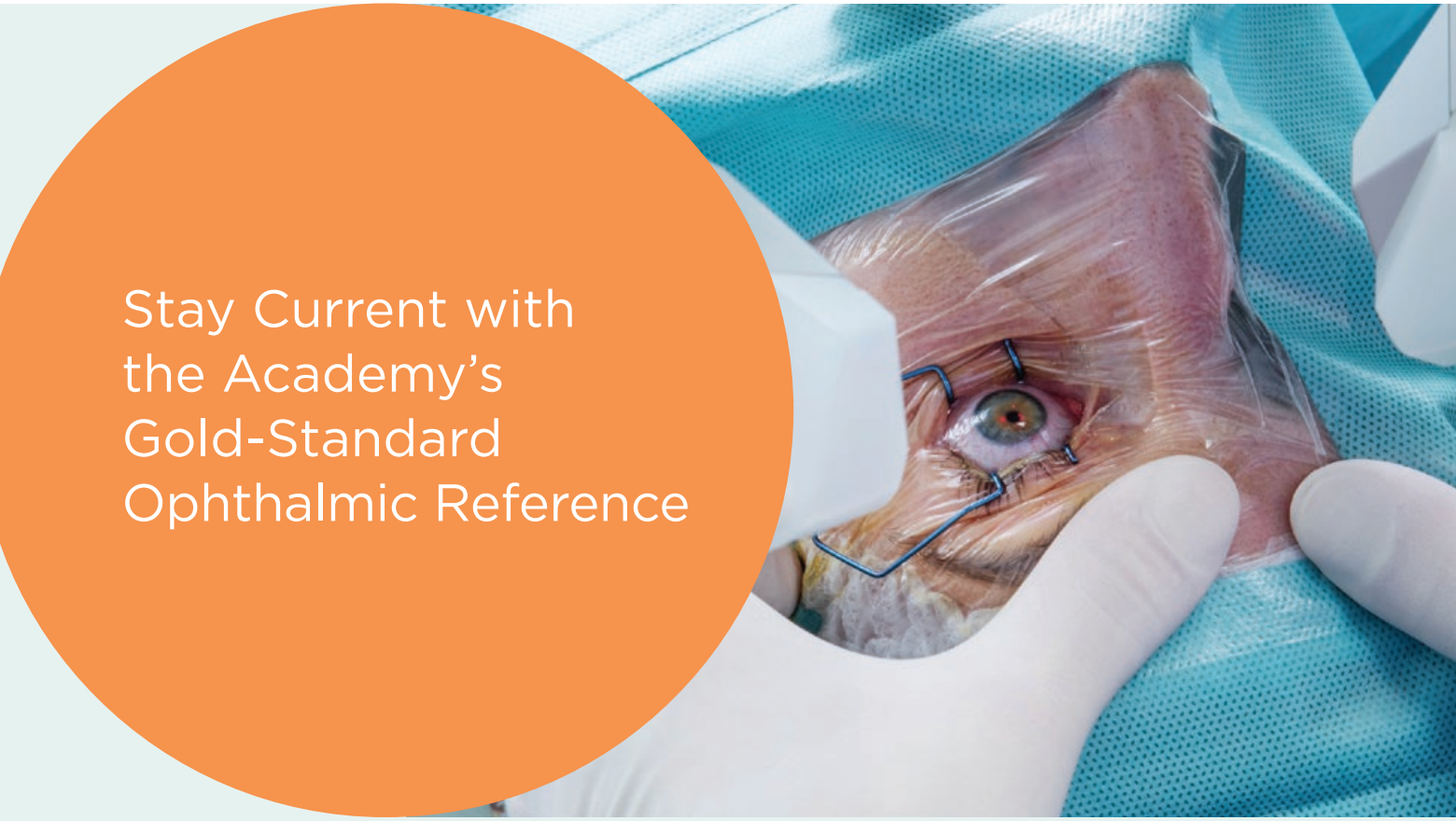

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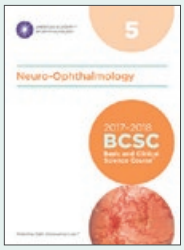

Major Revisions

Section 5: Neuro-Ophthalmology

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Section 13: Refractive Surgery

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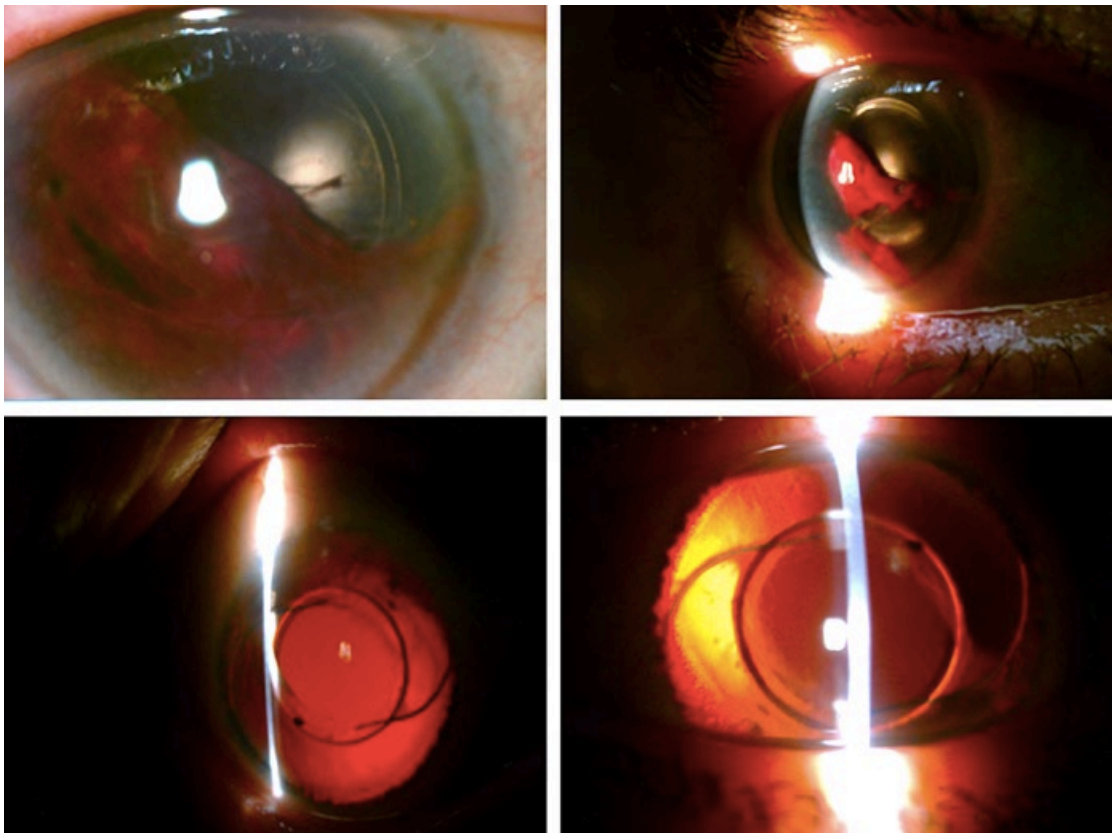
MYSTERY IMAGE

BLINK

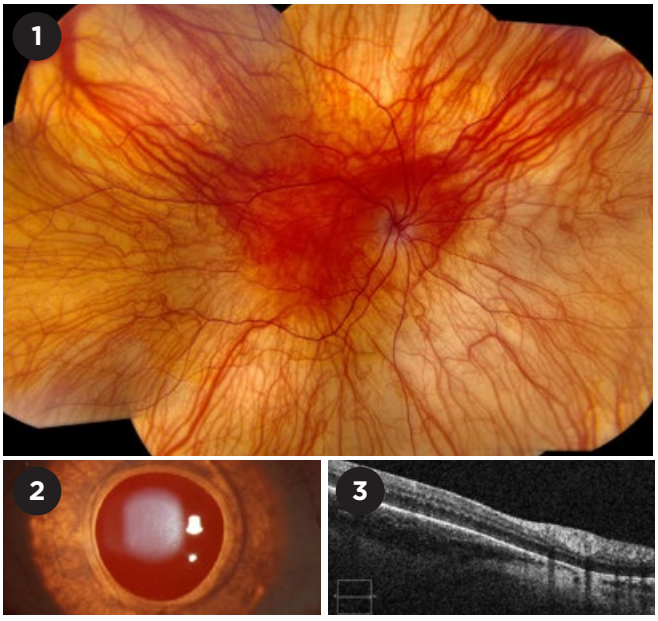


Henry D. Perry, MD, Ophthalmic Consultants of Long Island, Rockville Centre, N.Y.

WHAT IS THIS MONTH'S MYSTERY CONDITION? *Join the conversation at aao.org/eyenet, where you can post a comment on this image.*

LAST MONTH'S BLINK

Albinism



A 47-year-old woman underwent a routine ophthalmic evaluation for diabetic eye disease. She reported suffering from poor visual acuity and light sensitivity her entire life, but she had no recent changes in vision. The general physical examination revealed white hair and pale skin. Her best-corrected visual acuity measured 20/400 OU, and she had horizontal nystagmus. Color photographs of the fundus revealed an absence of pigmentation, and the choroidal vessels were easily visualized (Fig. 1). The slit-lamp examination showed hypopigmentation of the iris with transillumination throughout (Fig. 2). The fovea could not be found on optical coherence tomography scanning (Fig 3).

A more detailed medical history confirmed that the patient had oculocutaneous albinism. This autosomal recessive condition, characterized by decreased synthesis of melanin, affects 1 in 20,000 people. Ocular abnormalities are often noted at birth but remain stable throughout life.

WRITTEN BY **BY MICHAEL W. STEWART, MD,** AND **JASON CALHOUN,** MAYO CLINIC, JACKSONVILLE, FLA.

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 (2.7, 2.8) 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 (2.8 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
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South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(2) 2017

STRENGTH IN EVIDENCE

The efficacy and safety of LUCENTIS were rigorously studied in 10 clinical trials[1]*

LUCENTIS®
RANIBIZUMAB INJECTION

Approved for wet AMD, DR, DME, mCNV, and macular edema following RVO.

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

CONTRAINDICATIONS

- 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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- 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

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- 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 next page.

* The following randomized, double-masked clinical trials were conducted for the 5 LUCENTIS indications: **wAMD:** *MARINA*—Phase III, multicenter, 2-year, sham injection–controlled study; primary end point at 1 year. *ANCHOR*—Phase III, multicenter, 2-year, active treatment–controlled study; primary end point at 1 year. *PIER*—Phase IIIb, 2-year, sham injection–controlled study; primary end point at 1 year. *HARBOR*—Phase III, multicenter, 2-year, active treatment–controlled dose-response study; primary end point at 1 year. **DR and DME:** *RISE and RIDE*—Methodologically identical, Phase III, multicenter, 3-year, sham injection–controlled studies; primary end point at 2 years. *Protocol S*—Phase III, multicenter, 2-year, active-controlled study; key clinical outcomes at 2 years. **mCNV:** *RADIANCE*—Phase III, multicenter, 1-year, active-controlled study; key clinical outcomes at month 3. **RVO:** *BRAVO*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. *CRUISE*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months.[2-11]

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