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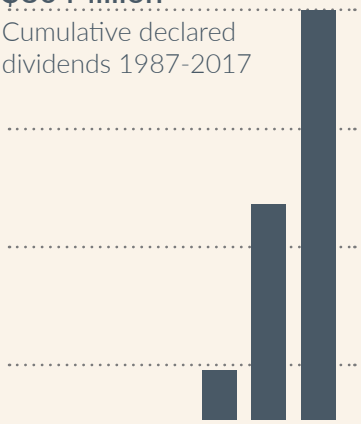

We are happy to announce another significant policyholder dividend equal to 15% of premium to be paid throughout 2019.

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Robert Wiggins, MD
Chair, Finance Committee and Treasurer

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

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

1 INDICATIONS AND USAGE

1.1 Ocular Surgery

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

1.2 Endogenous Anterior Uveitis

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Intraocular pressure (IOP) Increase

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

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

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

5.4 Bacterial Infections

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

5.5 Viral Infections

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

5.6 Fungal Infections

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

5.7 Topical Ophthalmic Use Only

DUREZOL is not indicated for intraocular administration.

5.8 Contact Lens Wear

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

6 ADVERSE REACTIONS

The following serious reactions are found elsewhere in the labeling:

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

6.1 Ocular Surgery

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

6.2 Endogenous Anterior Uveitis

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects

Pregnancy Category C

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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T2017-52
April 2017

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

One therapy for many eyes

DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a potent and effective ocular steroid that has been prescribed for millions of patients.[1,2]

In clinical studies of ocular surgery patients,

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

- 22% versus 8% on day 8
- 41% versus 12% on day 15

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

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

- 45% versus 25% on day 3
- 58% versus 27% on day 8
- 63% versus 35% on day 15

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

Average Co-Pay
<$42 with Commercial and Medicare Part D plans[3]

Eligible Commercial patients may pay as little as $30*

*Eligibility terms and conditions apply. Please see co-pay savings materials for details.

How could DUREZOL® Emulsion help more of your patients?

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

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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DUREZOL®
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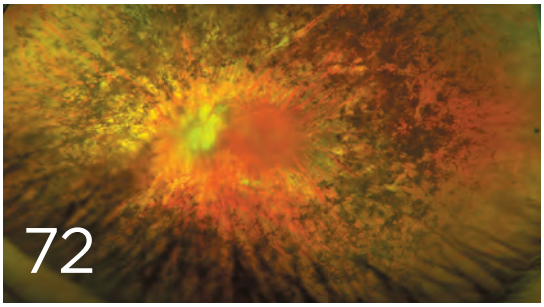

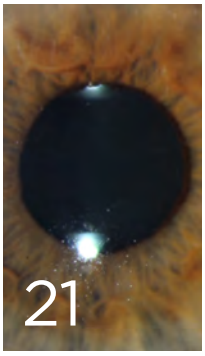

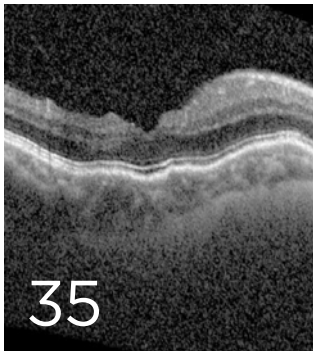

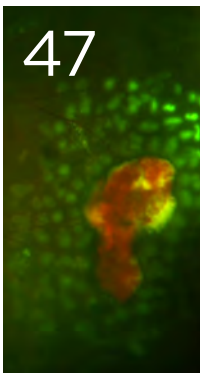

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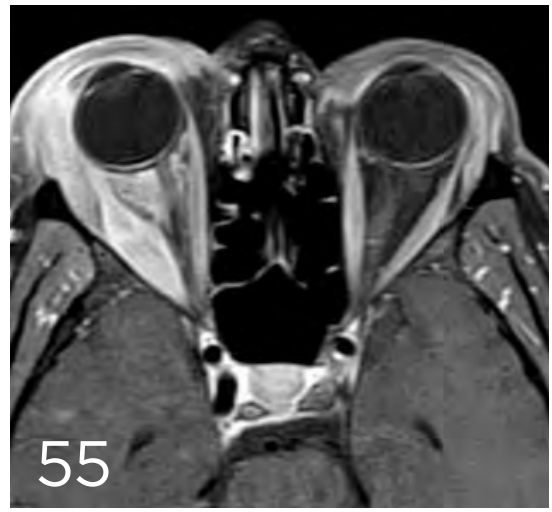

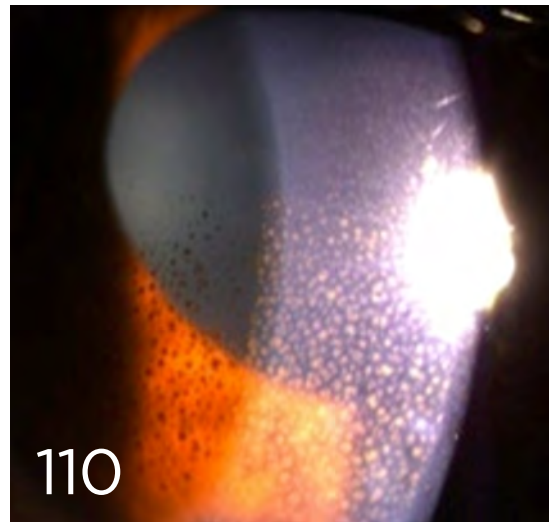

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Contributing Writers

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

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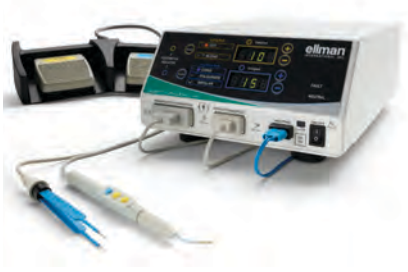

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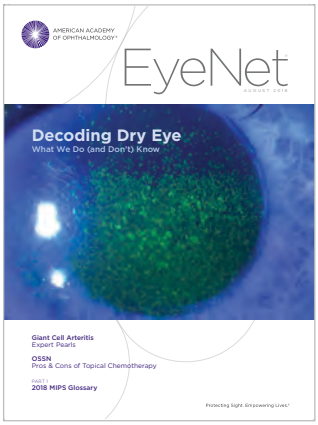
Letters

Single-Payer Health Care: The Next Logical Step

Reading "Single-Payer Health Care: Of Canada and California" (Current Perspective, August), I was struck by its alarmist tone.



Single-payer health care is suddenly looking attractive to Americans because of the failure of for-profit, private insurance–centered health care. Before the Affordable Care Act (ACA) was implemented in 2010, insurance prices were increasing exponentially; 15% (and quickly rising) of Americans were uninsured; medical bills caused most bankruptcies; quality remained the worst among comparable countries; and health care was reaching 20% of the federal budget and gross domestic product.[1]

With the ACA, we attempted a market-based approach. It stabilized prices, but its complexity and continued reliance on private insurance has doomed it. The Republican Party is dismantling ACA without any workable replacement.[2]

The type of single-payer coverage gaining most support is an improved "Medicare for all." Yes, taxes will go up, but Americans will no longer pay private insurance premiums, deductibles, copays, and coinsurance. Drug prices will fall.[1] People will pay about one-third less for health care overall.[1] Doctors and hospitals will enjoy a drop in administrative costs and malpractice insurance prices.[2] Medical students will pay much less for schooling and avoid the crush of student loans. Best of all, Americans will gain access to a higher quality of care, improving outcomes while decreasing costs.

Private insurance is just a middleman that moves money from the patient to the provider. Its real point is to make profits for shareholders, yet we are paying 30 cents of every health care dollar for administrative costs and insurance company profits instead of improving health.[1]

The single-payer form of universal coverage will come to the United States, as it remains the cheapest way to cover everyone. We see it succeeding in nearly every developed country of the world, and in the United States as Medicare, the government's most beloved program. Expanding Medicare to cover everyone is the next logical step.

Chandak Ghosh, MD, MPH
New York

1 Gaffney A. *J Policy Anal Manag.* 2018;37(3):188-195.
2 Woolhandler A, Himmelstein D. *Ann Intern Med.* 2017;166(8):587-588.

THE ACADEMY NEEDS YOUR INPUT. Sending a letter to *EyeNet* is just one of many ways to be heard. You also can contact your state, subspecialty, and specialized interest society's representative(s) on the Academy Council, which presents membership concerns to the Board of Trustees. Academy members also can register to attend the Oct. 28 Fall Council Meeting in Chicago.

To see a Council roster or register for the Fall Council Meeting, visit aao.org/council.

Progress for Inclusivity

"Cultivating Diversity in Ophthalmology" (Opinion, July) was very inspiring and I'm glad that it was shared throughout the Academy. Oftentimes underrepresented students are discouraged from applying to competitive specialties because they feel like it is an unattainable goal. Unfortunately, there is unconscious bias in the workforce in how minorities are represented. Preconceived notions often taint our awareness and beliefs toward other cultures and races. The opportunity for education in ophthalmology for minorities at Howard University is wonderful and definitely a step in the right direction for equal opportunity in employment.

Adriana H. Jones, BS
Plainfield, N.J.

Correction

In "Drug Update: Vyzulta and Rhopressa" (Clinical Update, September), it should be noted that Rhopressa's primary mechanism of action is lowering resistance to outflow through the trabecular meshwork. The article should have stated that Rhopressa "decreases [rather than promotes] actin-myosin contraction and reduces [rather than increases] actin stress fibers and focal adhesions in the trabecular meshwork to improve the outflow of aqueous humor."

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

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

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- Decreases use of pupil-expanding devices (epinephrine comparator)[2-7]
- Reduces surgical times (epinephrine comparator)[2,4,6,7]
- Prevents miosis during femtosecond laser-assisted surgery (epinephrine comparator)[5,8]
- Improves uncorrected visual acuity on day after surgery (epinephrine comparator)[2]
- Delivers NSAID to the anterior chamber and related structures better than routine preoperative topical drug administration, resulting in effectively complete postoperative inhibition of COX-1 and COX-2[9,10]

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Contact your OMIDRIA representative today or visit omidria.com to learn more

IMPORTANT SAFETY INFORMATION

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

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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Opinion

RUTH D. WILLIAMS, MD

What's an Ophthalmologist Doing on Instagram?

Remember when Instagram was a refreshing break from Facebook because it just showed pictures from friends? Well, Instagram—which now has over a billion active users—has morphed, as social media platforms are wont to do, and it's become a powerful venue for physicians to share medical information and engage with followers.

What exactly are ophthalmologists doing on Instagram? Many ophthalmology Instagram sites focus on education. For instance, Matt Weed, MD, shares photos, videos, and text about pediatric eye conditions (mattweed_eyedoctor). He recently posted a great video of a patient with spasmus nutans along with an explanation of the condition and its excellent prognosis. And while Rob Melendez, MD, MBA, the Academy's Secretary for Online Education, has an active social media presence on several platforms, he just started a separate Instagram site (eyeqdoctorrob) specifically to educate medical students, physicians, and the public.

Rupa Wong, MD, also started her blog (drrupawong) to educate her patients (and their parents) about pediatric ophthalmology, but it evolved into a mentoring site when young physicians began messaging her with questions about clinical practice, how to match in ophthalmology, or how she manages a private practice while raising 3 children. "Trainees may feel embarrassed to ask a senior attending about their work-life balance, but social media level that field and provide a platform to discuss sensitive topics."

Usiwoma Abugo, MD, an oculoplastics specialist, would agree. She designed her Instagram blog (mentormemd) specifically to mentor young physicians and medical students. Followers contact her through the blog for help with personal statements, resumes, and professional advice.

The site developed by Jesse Berry, MD, evolved the other way around. She initially started a fashion blog, she said, "because I found a void for fashion advice for professional women." However, as she blogged, she realized that people wanted more of a connection. "Readers wanted to see what I do, why I do it, and what's cool and unique about ophthalmology and ocular oncology." Now her blog (_moda_md) covers a blend of topics: fashion, lifestyle, art, travel, ocular oncology, what it's like to be an eye surgeon, and her research. "Because my blog is a platform for professionals to embrace their entire selves (in and out of the white coat), I need to include all those aspects."

Similarly, Andrea Tooley, MD, posts about her work along with her other passions of cooking and fitness (dr.andrea tooley). "I want to show that you can have a life outside of medicine but still be passionate and committed to your work."

Recognizing the power of social media to educate the public about eye issues, Steve Christiansen, MD, prepared a short video prior to last year's solar eclipse about the risks and prevention of solar retinopathy (eyestevemd). Between Facebook, Instagram, and YouTube, the video had over 100,000 views.

With such power to connect to users, physician Instagram bloggers have tremendous responsibility. Ophthalmologist-bloggers must be meticulous about HIPAA, professionalism, and accuracy. "Do not give medical advice," Rob advised. "You can use generalities about eye conditions, but always refer a person to their ophthalmologist or emergency room." The Academy developed a terrific Advisory Opinion on Social Media and Professionalism that discusses the nuances of physician responsibility.[1] And—in the latest development—the Academy has launched an Instagram account to complement its other social media channels. To check it out, go to aao.org/instagram.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Ophthalmologists who are on Instagram aren't just posting cool pictures and comments. Most are building a community around a common interest: ophthalmology. Usiwoma finds great satisfaction in providing mentorship and encouragement through her Instagram blog. She said, "As physicians, we add value to someone's life every day; my social media presence should do the same."

1 aao.org/ethics-detail/advisory-opinion-social-media-professionalism.

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Current Perspective

DAVID W. PARKE II, MD

ACOs: The One-Third of 1% Solution?

Health care expenditures in the United States are closing in on becoming one-fifth of our gross domestic product. In 2017, they totaled an estimated 3.49 trillion dollars—or $10,348 for every American. Over the past decade, they continued to grow faster than the rate of inflation.

A linchpin strategy for the Centers for Medicare & Medicaid Services (CMS) to reduce costs has been the Medicare Shared Savings Program's (MSSP) Accountable Care Organization (ACO), which was introduced as a part of the Affordable Care Act, or Obamacare. ACOs have been active since 2012. Loosely defined, they are groups of facilities and providers (including physicians) that agree to be held accountable to standards and processes for quality, cost, and experience of care for an assigned Medicare fee-for-service beneficiary population. They have different "tracks" that, among other things, define the amount of shared financial risk between CMS and the ACO. In 2018, MSSP ACOs provide care to 10.5 million (which is about 20% of) Medicare beneficiaries.

The ACO financial scorecard for 2017 is in. After more than 5 years, thousands of pages of enabling regulations, and millions of patients served, how have they done at reducing expenditures?

According to CMS, the 472 MSSP ACOs resulted in a net savings to CMS of $313.7 million. This sounds big, but let's put it in perspective. It is:

- 0.33% of the total spent on health care by the ACOs ($95 billion);
- a savings of $36 per ACO program Medicare beneficiary—a fraction of a single outpatient visit; and
- about the cost of 1 new F-22 fighter jet.

Let's put it in ophthalmologic terms. A 10% shift in anti-VEGF drug use for eye disease to lower-cost drugs would eclipse the entire net savings in all of the U.S. ACO program.

The ACO program is designed to encourage financial risk-taking. The more downside risk an organization assumes, the more upside benefit can accrue to it. It might therefore seem intuitive that the best-managed and most advanced ACOs (those that took on risk to reap greater financial rewards for themselves) would in fact spend less per beneficiary and save more for CMS. In fact, the reverse was true. Those that took downside risk spent $254 more per beneficiary than those that didn't! And 41% of the participating organizations actually increased Medicare spending. Yet, the 2019 proposed changes to the Medicare Quality Payment Program contain rules that are intended to accelerate the transition to downside risk.

Does this mean the ACO program is a failure and should be thrown on the health care reform trash heap? Advocates of ACOs would argue that—even though after 5 years the program has yet to generate a net financial benefit for Medicare—its performance in 2017 was the best year so far. The longer an ACO is in the MSSP, the more money it saves. In addition, advocates point to some encouraging quality metric data in measures such as reduction of hospital readmissions.

David W. Parke II, MD
Academy CEO

What does this all mean for ophthalmologists? Fewer than 70% of Medicare beneficiaries are enrolled in traditional fee-for-service Medicare (as opposed to Medicare Advantage). In the Quality Payment Program, although over 90% of specialists are in the Merit-Based Incentive Payment System, policy is intended to steer physicians to Alternative Payment Models—of which ACOs are supposed to be a dominant form. ACOs have complex and expensive standards for information technology, clinical and service standards, patient referral, and resource use. Internal guidelines for allocation of any shared savings generally are unfavorable to surgical specialists. As each ophthalmologist carefully weighs the pros and cons of participating in an ACO, we should all recognize that even after more than 5 years, the economic model remains unproven. Savings of less than one-third of 1% can hardly be considered a solution.

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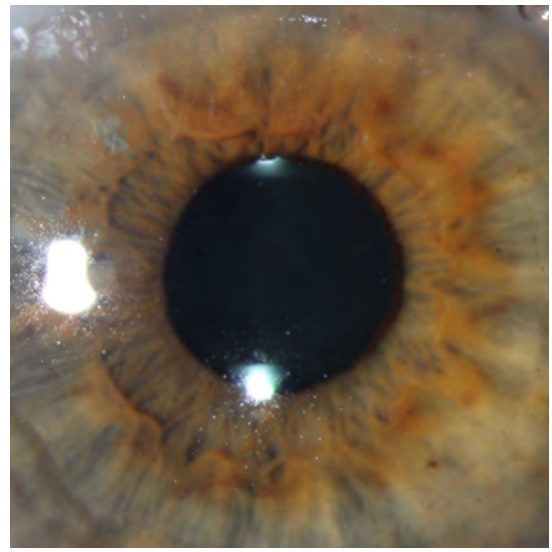
News in Review

COMMENTARY AND PERSPECTIVE

THIS MONTH, NEWS IN REVIEW HIGHLIGHTS SELECTED PAPERS from the original papers sessions at AAO 2018. Each was chosen by the session chair because it presents important news or illustrates a trend in the field. Only 4 subspecialties are included here; papers sessions will also be held in 5 other fields. For more information, see the Meeting Program, *which you'll find in your meeting bag, or the Mobile Meeting Guide (aao.org/mobile).*



DIABETIC DONOR. *This image was taken 10 years after surgery in a DSAEK donor who has diabetes.*

CORNEA PAPER

Cornea Grafts: Ensuring Success

GRAFT FAILURE AFTER DESCEMET stripping automated endothelial keratoplasty (DSAEK) is more likely if the donor has diabetes or pseudophakic/aphakic corneal edema (PACE) and if there were complications during the surgery, researchers in the Corneal Preservation Time Study (CPTS) have found.[1]

Building on previous evidence. Earlier reports from the CPTS showed that graft preservation time of up to 11 days did not impact the 3-year success rate of DSAEK[2] and that preservation time of up to 13 days did not affect endothelial cell loss.[3] In further analysis of data from this randomized, prospective clinical trial (1,330 eyes), the researchers looked for the influence on transplant success of secondary donor and recipient factors, said coauthor Mark A. Terry, MD, at the Devers Eye Institute in Portland, Oregon.

Risk of failure. The CPTS researchers found that early graft failure (within 8 weeks of surgery) was twice as likely if the donor tissue came from someone with diabetes and 4 times as likely if the recipient had a preoperative diagnosis of PACE. Even so, the 3-year graft success was over 90% when diabetic donor tissue was used and over 83% in recipients with PACE, Dr. Terry said.

Impact of operative factors. The analysis revealed that the surgeon's insertion technique did not matter but that surgical complications did, Dr. Terry said. "This study looked at many different ways of doing the surgery, and we found that it really doesn't matter what way you did the surgery, as long as you did the surgery well," he said. However, he added, "If the surgeon reported a complication during the surgery, those eyes had a highly statistically significant difference in success rates in terms of endothelial cell count and in terms of lasting 3 years."

Evidence-based road map. When these results are combined with the earlier CPTS results, cornea surgeons now have an evidence-based road map that can increase their chances of successful DSAEK, Dr. Terry said.

"These are the guidelines we're offering surgeons: We're telling them that their common preconceived notions of what constitutes the 'best' donor tissue is wrong—it turns out that age, storage time, and cell count of the donor tissue don't matter," he said.

Dr. Terry added, "Don't ask for young tissue; it doesn't make a difference. Don't ask for high endothelial cell counts; it doesn't make a difference. Don't ask for tissue that was harvested a day or 2 ago; it doesn't make a difference. Even the minimal standards set by the eye bank for quality donor tissue will yield excellent results in DSAEK surgery."

—Linda Roach

Factors Associated With Graft Success in the Cornea Preservation Time Study. ***When:*** *Monday, Oct. 29, during the second cornea original papers session (3:30-5:15 p.m.).* ***Where:*** *Room E450.* ***Access:*** *Free.*

Mark A. Terry, MD

1 Terry MA et al., on behalf of the Cornea Preservation Time Study Group. *Ophthalmology*. Published online Aug. 8, 2018.
2 Rosenwasser GO et al. *JAMA Ophthalmol.* 2017; 135:1401-1409.
3 Lass JH et al. *JAMA Ophthalmol.* 2017;135: 1394-1400.
Relevant financial disclosures—Dr. Terry: Bausch + Lomb: P,L; Envisia: C; Moria: L.

GLAUCOMA PAPER

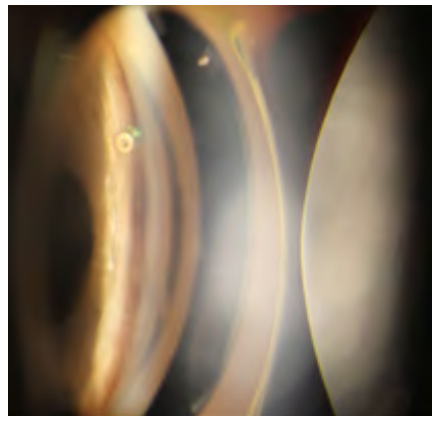
Sustained-Release Travoprost: Data at 12 Months

NO MORE BOTTLES, NO MORE DROPS. For glaucoma patients and their doctors, that dream came a bit closer to reality with the announcement that iDose (Glaukos), a travoprost-eluting intraocular implant, was safe and effective in patients with open-angle glaucoma or ocular hypertension during a phase 2 clinical trial.

"The early results are promising," said trial investigator John P. Berdahl, MD, with Vance Thompson Vision in Sioux Falls, South Dakota. Reduction in intraocular pressure (IOP) was sustained, he said, and the procedure was safe.

How it works. The iDose implant is filled with a proprietary formulation of travoprost that allows for consistent drug delivery and implanted in the angle during a microinvasive procedure. It continuously elutes therapeutic levels of travoprost for at least 1 year. Upon medication depletion, a new iDose is implanted and the old one is removed.

Study specifics. This prospective double-masked multicenter trial enrolled 154 patients who were on 0-3 glaucoma medications. Unmedicated mean diurnal IOP was 21-36 mm Hg in the study eye. Patients were randomized to 2 different eluting models of the delivery system—iDose-slow (n = 54) and iDose-fast (n = 51). Controls



IN PLACE. *This gonioscopic image shows the implanted iDose.*

(n = 49) received topical timolol ophthalmic solution 0.5% twice a day.

Findings. At 12 weeks, all study and control subjects achieved at least a 30% reduction in IOP. At 1 year, the subset of iDose eyes achieved a 33% reduction in IOP. Both the slow and fast models were equally efficacious. No adverse events, including hyperemia, were reported in either elution group.

Clinical implications. "Besides eliminating compliance issues, which are huge, we are glad to deliver the drug where we want it . . . inside the eye," Dr. Berdahl said. "We know that topical drops are tough on the ocular surface, but we are willing to pay that price to lower IOP. Now we won't have to."

Having said that, he noted that with drops, patients are confident they are receiving the drug. But how would a patient know when the implant runs out of the medication? He suggested that an iDose replacement strategy might need to be implemented to ensure an uninterrupted drug supply.

Dr. Berdahl also noted that, for the study, the iDose was implanted in the operating room. But, he said, "I can envision the possibility of an in-office procedure" at some point in the future.

Continuing investigation. For the next phase, 1,000 patients are being recruited for the phase 3 trial, which is looking at similar endpoints: IOP lowering and safety. And the phase 2 follow-up will continue through 3 years. In the meantime, Glaukos has begun seeking regulatory approvals for iDose travoprost in European markets and Japan. *—Miriam Karmel*

Interim Results of a Prospective, Randomized Phase 2 Study Evaluating the Safety and Efficacy of Novel Sustained-Release Travoprost Intraocular Implants. ***When:*** *Monday, Oct. 29, during the glaucoma original papers session (2:00-5:15 p.m.).* ***Where:*** *Room S404.* ***Access:*** *Free.*

Relevant financial disclosures—Dr. Berdahl: Glaukos: C.

NEURO-OPHTHALMOLOGY PAPER

Botox Effective for Dry Eye and Photophobia

DOCTORS HAVE BEEN USING BOT-ulinum toxin A (BoNT-A) to treat everything from facial wrinkles to strabismus. Now a study performed at the University of Miami supports adding photophobia and dry eye to the list, at least in patients with migraine.

"We found that dry eye symptoms, photophobia, and migraine pain severity were correlated and all improved following BoNT-A injection," said Ryan Diel, MD, now a resident in internal medicine and ophthalmology at the University of Iowa in Iowa City. "Dry eye and migraine were initially thought of as 2 different diseases and treated independently. But these findings suggest that the symptoms are linked and represent different manifestations of the same underlying disease."

A cohort study. For this study, 76 patients at the Miami Veterans Affairs Hospital with chronic migraine, for which BoNT-A is approved, were asked to assess the severity of migraine, photophobia, and dry eye symptoms prior to injection.

Then, 2 to 8 weeks postinjection, patients answered the same questions to assess treatment response. The researchers also evaluated whether preinjection tear volume, measured by the phenol red thread test (PRT), had any effect on symptoms.

Confirmatory findings. The study replicated findings of an earlier cross-sectional study at the same medical center.[1] Migraine, photophobia, and dry eye symptom scores were all sig-

John P. Berhdal, MD

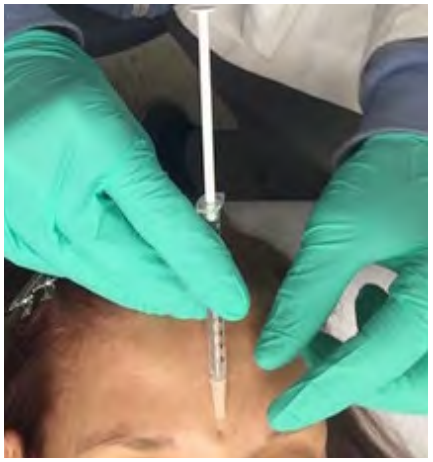
nificantly correlated, and symptoms improved following BoNT-A injections.

A surprise. However, PRT results did not correlate with symptom severity, meaning patients with photophobia and dry eye had relatively normal tear volume at baseline. "This suggests that the symptoms may not be related to abnormalities in the ocular surface," Dr. Diel said. In other words, patients with migraine may experience significant photophobia and dry eye symptoms despite relatively normal ocular surface parameters.

Looking ahead. In this study, patients received approved BoNT-A injections for chronic migraine. "The question is whether BoNT-A can be used in patients with dry eye not associated with migraine," Dr. Diel said. He plans to address that issue by using off-label BoNT-A injections in individuals who have dry eye and photophobia but are not affected by migraines.

"I hope that this and future studies will prompt physicians to consider new treatments for dry eye that is unresponsive to traditional therapies and in which neuropathic mechanisms are believed to underlie symptoms," he said.

—Miriam Karmel



INJECTION. *A patient receiving a BoNT-A injection in the procerus muscle, 1 of the muscles injected in the study protocol.*

OnabotulinumtoxinA Decreases Photophobia and Sensations of Dryness Independent of Tear Volume. *When: Tuesday, Oct. 30, during the neuro-ophthalmology original papers session (8:30-10:00 a.m.). **Where:** Room S405. **Access:** Free.*

1 Diel RJ et al. *Ophthalmology.* 2018;125(1):139-140.

Relevant financial disclosures—Dr. Diel: None.

UVEITIS PAPER

Macular Edema in NIU: New Rx, New Delivery Method

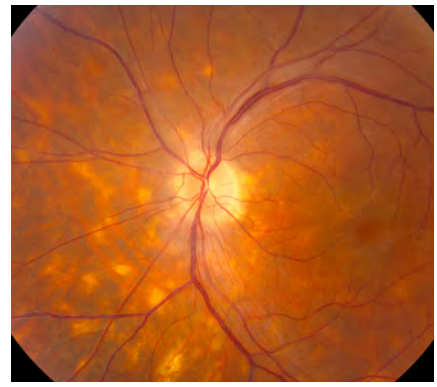
SUPRACHOROIDAL INJECTIONS OF A proprietary suspension of triamcinolone acetonide might present clinicians with a new treatment for the macular edema that can persist in patients with noninfectious uveitis (NIU) even after their inflammation is under control, according to the results of a phase 3 trial.

In the study, 46.9% of the patients who received a total of 2 suprachoroidal injections of the investigational new drug, CLS-TA (Clearside Biomedical) administered 12 weeks apart, gained at least 15 letters in best-corrected visual acuity at 24 weeks. That compared to 15.6% in the control subjects, who received sham injections, said Rahul N. Khurana, MD, with Northern California Retina Vitreous Associates in Mountain View, California.

Addressing an unmet need. This potential therapeutic approach would address a large unmet need in the treatment of patients with NIU, Dr. Khurana said.

"Uveitic macular edema is really challenging. It's the leading cause of vision loss in patients with uveitis," he said. "It occurs in about 40% of patients with uveitis, and it can be very difficult to manage even when you control the inflammation itself."

Novel method of drug delivery. "Most of our medicines for diseases of the posterior segment have centered on delivering medications in the intravitreal space. This is one of the first clinical trials, if not the first, to look at the suprachoroidal space," Dr. Khurana said. "So it's really exciting to see a suprachoroidal treatment actually work."



EDEMA. *This fundus image is of a patient with birdshot retinochoroidopathy (HLA-A29⁺) and cystoid macular edema.*

Measuring impact on vision. "This study was also unique in the sense that most uveitis studies evaluate a potential treatment's effectiveness at treating inflammation by measuring vitreous haze. But in this study we actually looked at improvements in vision," he said.

If CLS-TA ultimately wins marketing approval from the U.S. Food and Drug Administration, it has the potential to become a new paradigm for the treatment of visual impairment caused by uveitic macular edema, Dr. Khurana concluded.

—Linda Roach

Relevant financial disclosures—Dr. Khurana: Allergan: C; Clearside Biomedical: S; Genentech: C; Regeneron: C,S.

Phase 3 Efficacy Data of Suprachoroidally Injected CLS-TA for Macular Edema due to Noninfectious Uveitis. *When: Monday, Oct. 29, during the uveitis original papers session (8:30-10:00 a.m.). **Where:** Room S405. **Access:** Free.*

POSTERS AT THE MEETING

For a look at cutting-edge research, visit the Scientific Poster Theater. ***When:*** *For times, check the Mobile Meeting Guide at aao.org/mobile.* ***Where:*** *South Hall A.* ***Access:*** *Free.*

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

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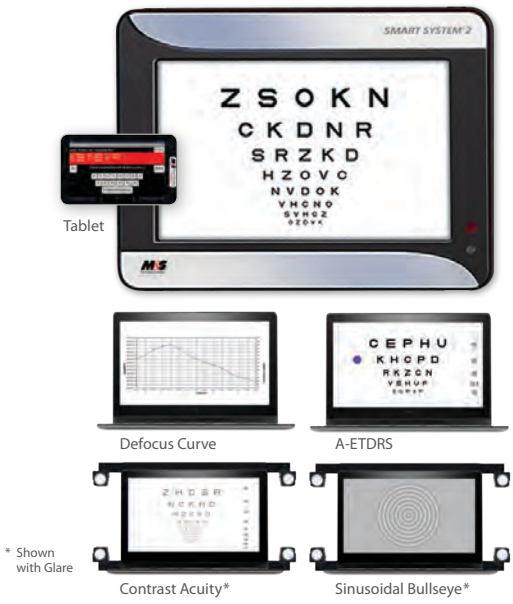

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Diana R. Shiba, Academy fellow since 2010, shares an uplifting moment with her patient. The Academy's IRIS Registry aggregates patient data to facilitate new scientific discoveries.

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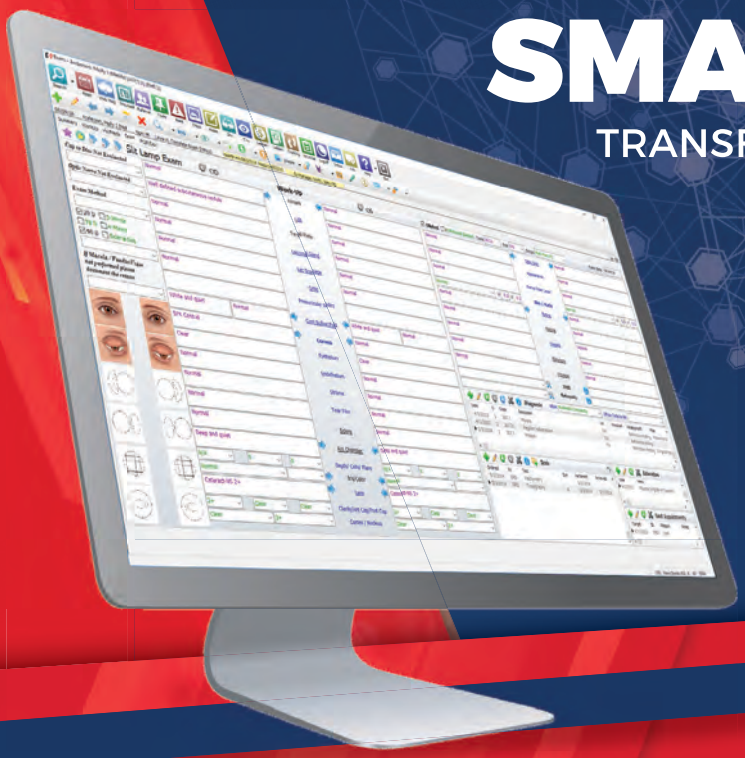

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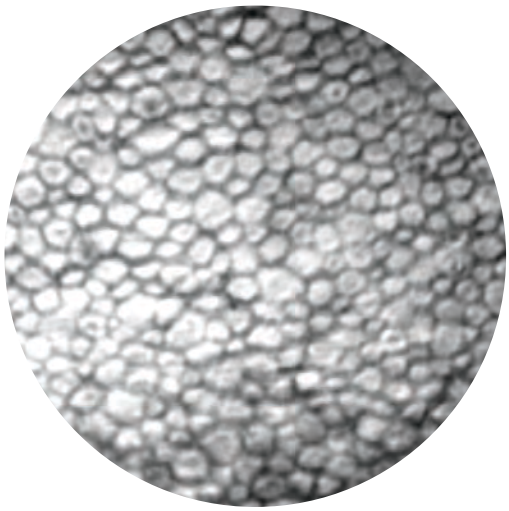

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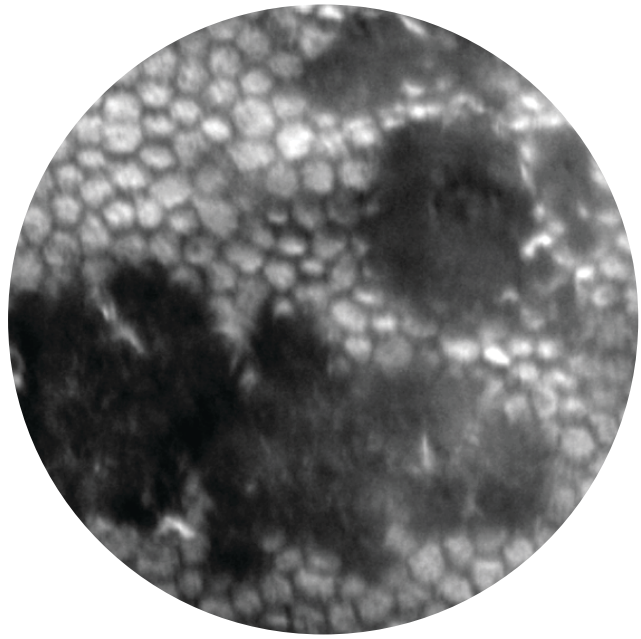

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

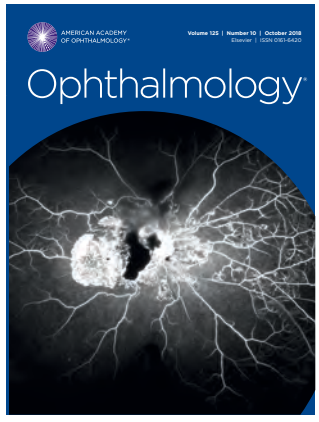
Ophthalmology

Selected by Stephen D. McLeod, MD

Emixustat for Geographic Atrophy Secondary to AMD

October 2018

Rosenfeld et al. evaluated the use of emixustat hydrochloride in the management of geographic atrophy (GA). They found that emixustat did not reduce the growth rate of GA—and that the most common adverse events were ocular in nature and likely attributable to the drug's mechanism of action.



Enrollees (N = 508) had GA secondary to age-related macular degeneration (AMD), total GA area ranging from 1.25 to 18 mm^2, and a visual acuity score of at least 35 letters. Participants were assigned randomly (1:1:1:1) to receive placebo or emixustat (2.5, 5, or 10 mg) administered orally, once daily, for 24 months. Evaluations were conducted from screening through month 25. The primary efficacy endpoint was the mean annual growth rate of total GA area, which was measured from fundus autofluorescence images at a central reading center. Also measured was the change from baseline in normal luminance best-corrected visual acuity (NL-BCVA). Safety and tolerability were determined by documenting adverse effects, measuring vital signs, and reviewing findings from lab tests and physical exams.

The study was completed by 320 patients (63%). Demographics and baseline characteristics were comparable among the 4 groups. During the study, average GA growth rates were similar with placebo and emixustat (placebo: 1.69 mm^2 per year; emixustat groups: 1.69-1.84 mm^2 per year). Changes in NL-BCVA also were comparable among the study groups. Subjects whose low luminance deficit (LLD) was larger at baseline (≥20 letters) had faster GA growth during the 24-month treatment period. No meaningful association was observed between GA growth rate and the risk-allele status of the AMD-associated single-nucleotide polymorphisms that were tested.

The most common adverse events in patients treated with emixustat were delayed dark adaptation (55%), chromatopsia (18%), visual impairment (15%), and erythropsia (15%).

The authors noted that this research sheds further light on the natural history of GA and confirms previously observed links between certain baseline traits and the rate of GA growth. Even though emixustat was not effective in their study, robust safety data were gained that may be relevant to other indications for emixustat.

Topical Ocular Glucocorticoids Cause Adrenal Suppression in Infants

October 2018

Bangsgaard et al. assessed adrenal suppression among infants who received topical ocular glucocorticoids (GCs) following surgery for congenital cataract. They found that two-thirds of their study population experienced this adverse effect, which correlated strongly with high cumulative doses.

This retrospective, consecutive case series included patients under 2 years of age who underwent surgery at Copenhagen University Hospital in Denmark. The surgical procedure and GC dosing protocol were standard. The authors reviewed patients' records and documented outcomes, GC dose per kg of body weight, and the timing of a standard corticotropin (adrenocorticotropic hormone) stimulation test. The main outcome measure was the incidence of adrenal suppression among infants who were tested for it during GC treatment.

Of the 26 infants who underwent the surgery, 15 (58%) received the corticotropin stimulation test while on GC treatment. Ten (67%) of the 15 infants had adrenal suppression, and the degree of suppression varied widely. Two of these displayed obvious clinical signs of Cushing syndrome, and another had signs of Addisonian crisis while under general anesthesia. Adrenal suppression was treated with hydrocortisone replacement therapy. In the 5 days preceding testing, cumulative GC doses per body

weight were significantly higher for the patients with suppressed adrenal function. Recovery of adrenal function occurred after a median of 3.1 months (range, 2.3 months to 2.3 years).

Eleven (42%) of the 26 infants were tested later, at a median of 21 days (range, 6-89 days) after cessation of GC treatment. All test results were normal at that time.

The authors advocate using the lowest possible dose of topical ocular GCs for the shortest period needed to control inflammation postoperatively. They also advise systematic assessment of adrenal function when standard GC protocols are utilized, along with careful evaluation of other dosing regimens. *(Also see related commentary by Scott R. Lambert, MD, in the same issue.)*

Prolonged Reading Worsens Dry Eye Symptoms

October 2018

Karakus et al. studied the effects of prolonged silent reading on tear film and ocular surface parameters. They found that symptoms of dry eye disease (DED) provoked by everyday tasks, such as reading for pleasure or work, often go undetected during clinical testing.

This prospective observational study included 177 patients with DED and 34 normal controls, all of whom were at least 50 years old. After symptom evaluation with the Ocular Surface Disease Index (OSDI) questionnaire, the following tests were performed in consecutive order: automated noninvasive tear breakup time (TBUT), surface asymmetry and regularity indexes, Schirmer test (without anesthesia), corneal staining using fluorescein, and conjunctival staining using lissamine green. The participants then completed a standardized validated task consisting of reading a 7,200-word story for at least 30 minutes.

The same tests were repeated after the reading exercise, and the researchers documented differences in the 2 sets of test results.

After the reading task, all test results were poorer in both study groups, except for the surface asymmetry index. The worsening was significant for corneal and conjunctival staining in the DED group and for corneal staining in the control group.

At baseline, OSDI correlated only with scores for corneal staining and conjunctival staining. Among the measurements taken after reading, baseline OSDI correlated with TBUT and with scores for corneal staining and conjunctival staining. Changes in TBUT and Schirmer test findings correlated strongly with their respective baseline values, indicating that patients with greater tear film instability and lower aqueous tear secretion are more susceptible to worsening symptoms after reading. Worsening corneal staining results correlated with the baseline conjunctival staining values and surface regularity index.

The authors advocate use of the OSDI for more precise quantification of dry eye symptoms, particularly in clinical studies involving treatment comparisons. They also suggest that patients' dry eye symptoms be quantified after a period of silent reading, rather than at rest. *(Also see related commentary by Saaeha Rauz, PhD, FRCOphth, in the same issue.)*

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

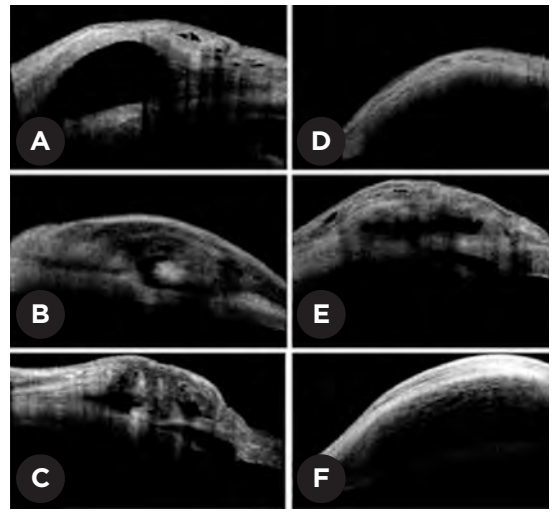
Selected by Henry D. Jampel, MD, MHS

Ologen Implant After Trabeculectomy

September/October 2018

Does the biodegradable collagen matrix implant (Ologen) further the success of trabeculectomy? Findings from the first randomized controlled trial to address this question indicate that it does not.

Sen et al. set out to compare the success of trabeculectomy performed with and without the Ologen implant, which is being investigated as a substitute or an adjunct for antimetabolites such as mitomycin C (MMC).



BLEB ANALYSIS. *All images on the left are of patients who received MMC alone; images on the right are of those who received MMC and the Ologen implant. No side effects linked to the implant were noted.*

For this study, the researchers recruited 50 patients (50 eyes), all of whom were Asians from north India, and assigned them to undergo either trabeculectomy with low-dose MMC (1 mg/mL, administered for 1 minute) alone or trabeculectomy plus low-dose MMC and the Ologen implant. The primary outcome was the percentage reduction in intraocular pressure (IOP); secondary outcomes included the percentage of patients achieving absolute and qualified success for IOP <15 mm Hg and <18 mm Hg; the postoperative need for glaucoma medications; and the rate of postsurgical complications.

At 12 months' follow-up, 22 eyes remained in the MMC group, and 23 remained in the MMC–Ologen group. In the MMC group, IOP was 25.96 ± 4.82 mm Hg preoperatively and dropped to 11.33 ± 3.81 mm Hg postoperatively. In comparison, preoperative IOP in the MMC–Ologen group was 26.32 ± 4.27 mm Hg; this dropped to 14.35 ± 3.34 mm Hg postoperatively. Greater IOP reduction was noted in the MMC group at the 6- and 12-month marks (56.9% and 55%, respectively) than in the MMC–Ologen group (47.1% and 44.2%). When an IOP of ≤15 mm Hg was considered as the definition of success, cumulative success was achieved in 86.5% of MMC eyes

and in 73.9% of MMC–Ologen eyes.

Medication outcomes were similar between the 2 groups at the 12-month mark—17 of the 22 remaining patients in the MMC group were off glaucoma medications at this point, versus 18 of the 23 in the MMC–Ologen group. Similarly, no significant differences were noted between the 2 groups in terms of complication rates.

The authors stated that, given the homogenous nature of their patient population, the implant should be evaluated in a more heterogenous population with different ethnicities represented. Nonetheless, they said, despite the theoretical advantages of the implant, it appears to offer no practical advantage. *—Summary by Jean Shaw*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Macular Atrophy in Wet AMD

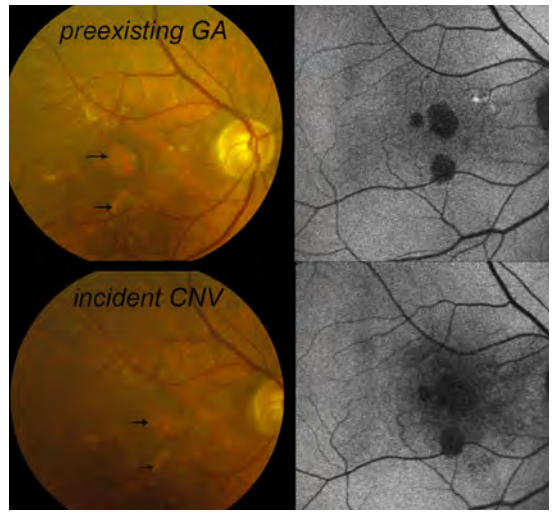
October 2018

Domalpally et al. investigated the prevalence of macular retinal pigment epithelial atrophy in eyes with recently diagnosed neovascular age-related macular degeneration (AMD). In addition, they assessed imaging characteristics in 3 groups of patients: 1) those with macular atrophy before the onset of choroidal neovascularization (CNV), 2) those with macular atrophy concomitant to CNV diagnosis, and 3) those who developed macular atrophy during follow-up of CNV. They found that macular atrophy is common in neovascular AMD and often can be attributed to preexisting geographic atrophy (GA). In addition, they found that the presence of macular atrophy is an indicator of poor visual prognosis.

For this cohort study, the researchers evaluated participants of the AREDS2 FAF (Age-Related Eye Disease Study 2 fundus autofluorescence) ancillary study. AREDS2 FAF included 2,509 participants (4,328 eyes) at risk of developing advanced AMD. Color photographs and FAF images were evaluated in those who developed CNV. The main outcome measures were the incidence and enlargement rate of macular atrophy and visual acuity (VA) changes in eyes with incident CNV.

Over 4 years, incident CNV developed in 334 of the 4,328 eyes. Of these, 137 eyes (41%) had macular atrophy at the event visit (defined as the point at which CNV was identified by the image reading center)—and of those 137 eyes, half had preexisting GA. Of the 197 eyes (59%) that did not have macular atrophy at the event visit, 49 developed it during follow-up.

The mean area of macular atrophy was largest in eyes with preexisting GA and CNV, and macular atrophy involved the center of the macula in over two-thirds of all eyes. With regard to VA, by 3 years of follow-up, eyes with macular atrophy had lost a mean of 10.9 letters, while those without it had lost a mean of 3.7 letters. *—Summary by Jean Shaw*



COMPARISON. *Color and autofluorescence images showing GA (top) in an eye that developed wet AMD at the next annual visit (bottom).*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Povidone-Iodine Plus Dexamethasone for Adenoviral Conjunctivitis

October 2018

There are currently no approved medications for treating adenoviral conjunctivitis. **Pepose et al.** found a promising option in a topical ophthalmic suspension of povidone-iodine (PVP-I) 0.6% and dexamethasone 0.1%.

This multicenter, double-masked trial included 144 Indian adult patients with a positive AdenoPlus test. The researchers randomized this cohort to either PVP-I plus dexamethasone (n = 48), PVP-I alone (n = 50), or vehicle (n = 46). The 3 groups were then monitored 3, 6, and 12 days after treatment for both clinical resolution (the absence of watery conjunctival discharge and redness) and virus eradication (negative cell culture assay).

The proportion of patients with clinical resolution at the day 6 visit was 31.3% in the PVP-I–dexamethasone group, which was significantly higher than that observed in the vehicle group (10.9%) and numerically higher compared with PVP-I alone (18.0%). The results for complete eradication of the adenovirus were similar. At day 6, the proportion of patients with a negative cell culture assay was 79.2% after treatment with PVP-I plus dexamethasone, significantly higher than with vehicle (56.5%) and numerically higher compared with PVP-I alone (62.0%).

The authors also noted minimal safety concerns with the use of PVP-I plus dexamethasone. Phase 3 studies to further evaluate the safety and efficacy of this treatment are currently underway.

Endophthalmitis Following Bilateral Same-Day Anti-VEGF Injection

October 2018

The most common indications for intravitreal anti–vascular endothelial growth factor (VEGF) therapy often require chronic treatment in both eyes. As a result, retina specialists routinely opt for bilateral same-day injections to reduce the number of office visits necessary for patients. Many clinicians, however, avoid this protocol for fear of bilateral endophthalmitis. To alleviate such concerns, **Borkar et al.** examined the results of more than 100,000 anti-VEGF injections and found low rates of infection.

This retrospective cohort study included a review of a private practice's records for all bilateral same-day anti-VEGF injections performed from 2012 to 2017. The researchers collected demographic information for all patients as well as information relating to presentation examination, culture data, and visual outcomes.

During the 5-year span, the practice performed 101,932 bilateral same-day injections for 5,890 patients during 50,966 office visits. The number of these injections increased from approximately 870 injections per month in 2012 to 2,300 in 2017. Neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME) were the most common indications for treatment. The most common agent used for neovascular AMD was ranibizumab. Aflibercept was the most common drug used for DME.

In total, the authors identified 28 cases (0.027%) of unilateral endophthalmitis—approximately 1 in 3,700 injections—and found no instances of bilateral endophthalmitis. No patient experienced more than a single occurrence.

These results, the authors noted, demonstrate the safety of bilateral same-day anti-VEGF injections when extreme caution is taken to prevent infection—a finding that is especially important as the number of patients requiring anti-VEGF treatment continues to grow. —*Summaries by Mike Mott*

JAMA Ophthalmology

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

Cataract Surgery and the Rate of Traffic Accidents

September 2018

Cataracts are a leading cause of impaired vision worldwide. But do they increase the risk of serious traffic accidents? In a population-based study, **Schlenker et al.** examined the records of >500,000 patients and found that cataract surgery was associated with a reduced rate of hospital visits due to a traffic crash when the cataract surgery patient was the driver.

This study included Canadian patients 65 years and older who underwent their first cataract surgery between 2006 and 2016. Each patient's record was tracked for up to 5 years after cataract surgery. The researchers excluded those patients who had cataract surgery combined with retina, glaucoma, or cornea surgery because of uncertain visual recovery.

The mean age of the 559,546 patients was 76 years, and 58% were women. Almost no patient had received a medical warning from his or her physician regarding fitness to operate a vehicle noted in the record. A total of 4,680 traffic crashes occurred during the baseline interval, and 1,200 traffic crashes took place during the follow-up after cataract surgery. This reduction represented 0.22 fewer crashes per 1,000 patient-years when the patient was the driver. No reduction in crashes was observed in other secondary outcomes, including traffic accidents in which the patient was a passenger or pedestrian. With regard to patient subgroups, the researchers found that patients who were younger, were male, had more emergency visits in general, and had more frequent outpatient physician visits were at greater risk of traffic crashes when driving.

These results suggest that improvements in vision following cataract surgery are associated with decreased driving risks. The researchers also noted postsurgery crash rates were highest in the first month, perhaps owing to uncorrected refractive error, adapting to recovery, or overconfidence—a finding that should inform postsurgery physician counseling.

Enhanced Screening Model for Retinopathy of Prematurity

September 2018

Current screening criteria for retinopathy of prematurity (ROP) are predominantly based on birth weight (BW) and gestational age (GA) and have low predictive value for identifying infants who are at risk for severe cases. To improve ROP screening specificity and sensitivity, **Binenbaum et al.** proposed a new set of criteria combining BW, GA, and postnatal weight gain.

The retrospective Postnatal Growth and ROP Study included 6-year data on 7,483 premature infants from the United States and Canada who were examined for ROP and had a known ROP outcome. The researchers developed a hybrid predictive model to apply to this data, which combined common BW and GA thresholds with a comparison with expected growth from infants without ROP, an assessment of multiple growth intervals, and a consideration of nonphysiological weight gain.

Their final model consisted of the following 6 screening criteria:

- a BW of <1,051 g;
- a GA of <28 weeks;
- a weight gain of <120 g during days 10-19 after birth, <180 g during days 20-29, or <170 g during days 30-39; and
- hydrocephalus diagnosed on brain imaging study.

Applied in this fashion to the 6-year data, the researchers' model accurately predicted 459 of 459 infants with type 1 ROP, 466 of 472 with type 2 ROP, and 524 of 524 treated for ROP. It also reduced the number of unnecessary examinations by 2,269.

According to the authors, these criteria predict the development of severe ROP with a greater specificity and sensitivity than do current screening methods. And because the model uses routinely collected data and requires minimal calculation, it would have a minimal impact on workflow in neonatal intensive care units.

The Influence of Visual Impairment on Cognitive Function

September 2018

Worsening vision and declining cognitive function are common among the elderly. To better understand the relationship between the 2 conditions, **Zheng et al.** conducted a population-based study of older U.S. adults and found that visual impairment might have a substantially large influence on declining mental abilities.

For this study, the researchers evaluated 2,520 adults aged 65 to 84 in 4 rounds across a 4-year period. Outcome

measures included visual acuity (VA) via Early Treatment Diabetic Retinopathy Study (ETDRS) charts and cognitive status via the Mini-Mental State Examination (MMSE).

Both VA and MMSE scores worsened over time. The average biannual decline of VA was 0.022 logMAR, and the average annual decline in VA was 0.011 logMAR—an annual loss of less than 1 letter on the ETDRS acuity chart, or roughly 1 line over 8 years. For the MMSE score, the average biannual decline was −0.59.

The researchers also looked at the VA and MMSE relationship longitudinally and found that the rate of worsening VA was associated with the rate of declining MMSE score: For example, VA in the previous rounds of examination were associated with MMSE scores in subsequent rounds, and vice versa. However, the impact of VA on the MMSE scores was larger and stronger than the reverse, demonstrating that vision is likely the driving force in this dynamic relationship.

This longitudinal association between vision and cognitive function suggests that maintaining good vision could be an important strategy for minimizing age-related cognitive change. *(Also see related commentary by Paul J. Foster, PhD, FRCS (Ed), Sharon Y.L. Chua, PhD, and Axel Petzold, MD, PhD, in the same issue.)*

—Summaries by Mike Mott

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Cost-Effectiveness of Intracameral Moxifloxacin

Journal of Cataract & Refractive Surgery
2018;44(8):971-978

Using recent data and different payer perspectives, **Leung et al.** compared adjuvant intracameral (IC) moxifloxacin plus perioperative topical antibiotic treatment against standard prophylaxis (i.e., topical antibiotics) to assess cost-effectiveness for endophthalmitis prevention after cataract surgery. They found that, despite the rising cost of IC moxifloxacin, the drug can be cost-effective as well as cost-saving from the U.S. societal perspective. However, from the standpoint of the health care sector, the drug was cost-effective but not cost-saving.

The researchers calculated incremental cost-effectiveness ratios (ICER) and incremental cost-utility ratios (ICUR) for 2 groups of patients: 1) Those who received standard prophylaxis and 2) those who received standard prophylaxis plus IC moxifloxacin. The base case was a healthy 73-year-old man with bilateral cataracts undergoing uncomplicated first-eye surgery. Incidence and cost data were derived from results of a PubMed search in addition to Medicare reimbursement rates and average wholesale drug prices. All costs and benefits were adjusted by 3% annually and for inflation. To assess uncertainty, the authors performed deterministic and probabilistic sensitivity analyses.

Their results showed that, compared with standard prophylaxis, an adjuvant 500 µg of IC moxifloxacin (for $20) was cost-saving from a societal standpoint in the base case. In probabilistic sensitivity analyses, all values were within the societal willingness-to-pay threshold of $50,000 per quality-adjusted life year (QALY). Of 10,000 iterations, 6,142 (61%) were cost-saving. Although IC moxifloxacin at this price point was cost-effective from the health care sector perspective (ICUR of $8,275 per QALY), it was cost-saving only in cases with posterior capsule tear. Adjuvant IC moxifloxacin was superior to topical antibiotics for improving QALYs.

According to this study, the price tag for 500 µg of IC moxifloxacin would need to be less than $22.20 to achieve societal cost-saving and less than $9.20 for health care sector cost-saving.

Low-Dose Hyaluronidase for Reduction of HA Nodules

JAMA Dermatology
2018;154(7):765-772

In the first randomized study to evaluate the issue, **Alam et al.** tested the effectiveness of low-dose hyaluronidase to reduce aliquots of hyaluronic acid (HA) filler that had been injected into patients' arms. They found that very small doses permitted dissolution of minute quantities of HA filler and eliminated the need to remove the entire implant. This indicates a potential role for low-dose hyaluronidase in resolving minor asymmetries that may occur with such fillers, as can occur with injections in the periorbital area.

This study was a split-arm, parallel-group randomized trial of 72 injection sites among 9 women (mean age, 45.8 years). Aliquots of Juvéderm Ultra XC (Allergan) or Restylane-L (Galderma) were injected bilaterally into the upper inner arms of each participant. At 1, 2, and 3 weeks following the injections, each injection site received a constant volume (0.1 mL) of variable-dose hyaluronidase (1.5, 3.0, or 9.0 U per 0.1 mL) or saline control.

At both the 4-week and 4-month marks, physician assessments of filler detectability were significantly different for saline and hyaluronidase. Findings were similar for subjects' self-assessments. The areas that received 9.0 U of hyaluronidase were significantly less palpable than those that received 1.5 U. Dose dependence was more common with Restylane-L.

Although very small doses of hyaluronidase can disintegrate HA, slightly higher doses usually provide faster dissolution. Low doses may be effective if only subtle changes are needed, such as refining contour. The low-dose strategy may be more appropriate, convenient, and satisfying for certain patients.

—Summaries by Lynda Seminara

Trabeculectomy-Induced Hypotony: When and How to Intervene

Ocular hypotony is a relatively common consequence of trabeculectomy, but is it always a problem? The reality is that an intraocular pressure (IOP) that is harmfully low in one patient can be innocuous, or even beneficial, in another.

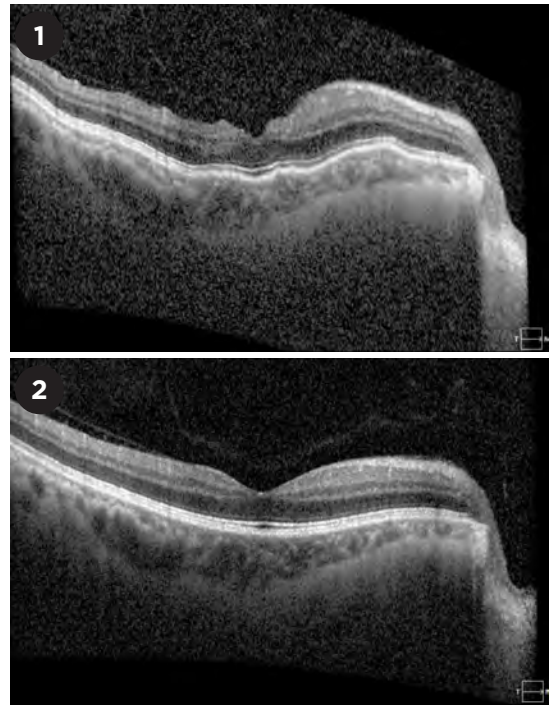
Joseph Caprioli, MD, at the University of California, Los Angeles, said, "In some patients, detrimental effects of hypotony, such as maculopathy, occur at a pressure of 8 or 10 mm Hg. Others can have a pressure of 2 mm Hg and the eye functions well. I wouldn't consider these latter patients to be physiologically hypotonous, and a pressure of 2 mm Hg is probably very good for their glaucoma." Joel Schuman, MD, at the New York University School of Medicine, noted, "It depends on the patient as to whether the eye can withstand a certain pressure, be it too high or too low."

When it comes to managing patients with trabeculectomy-induced hypotony, some questions to consider include the following: How frequently should you monitor? When should you intervene? And which surgical procedures yield the best results?

Hypotony and Its Pathophysiology

Hypotony has commonly been considered to be an IOP of 6.5 mm Hg or less, which is >3 standard deviations below the mean for nonglaucomatous eyes.[1] The use of antifibrotic agents such as mitomycin C (MMC) during trabeculectomy has coincided with an increase in rates of postsurgical hypotony.[2] Recent reports indicate that the rate of hypotony after trabeculectomy is variable and difficult to predict, ranging from slightly less than 2%[3] to more than 40%.[4]

Pathophysiology. In practice, the numeric definition of hypotony does not necessarily correspond to poor outcomes.[3] Dr. Schuman said, "If the patient is tolerating the low pressure, hypotony in and of itself is not a reason to intervene." In a retrospective case-control study, Tseng et al.[3] determined that patients who experienced hypotony after trabeculectomy (defined as IOP ≤5 mm Hg at ≥3 months postoperatively) shared similarities with those who did not, including reoperation rate, vision loss, and bleb-related infection. Dr. Caprioli, who coauthored that study, said he prefers the following pathophysiologic definition of hypotony: "the pressure that causes secondary changes in the eye, such as swelling in the retina, swelling of the optic disc, folds in the choroid, and folds and swelling of the cornea." These secondary changes signal that the patient has hypotony maculopathy, a worrisome complication of hypotony.



POSTOP VIEWS. *Signs of hypotony maculopathy depicted by optical coherence tomography (1) after primary trabeculectomy and (2) following subsequent bleb revision to raise IOP. The images were obtained 10 months apart.*

Hypotony maculopathy. Hypotony maculopathy involves chorioretinal wrinkling, papilledema, vascular tortuosity, and vision loss.[5] If left untreated, these structural and functional effects can become irreversible. To correct hypotony maculopathy, the IOP must

BY JENNIFER S. GRIFFIN, MS, CONTRIBUTING WRITER, INTERVIEWING **JOSEPH CAPRIOLI, MD, CATHERINE GREEN, FRANZCO,** AND **JOEL SCHUMAN, MD.**

Joseph Caprioli, MD

be raised, which presents a challenge to glaucoma surgeons. "You want to raise the pressure so that it causes the maculopathy to resolve but does not add to the risk of glaucomatous progression," said Dr. Caprioli.

Target Setting

The experts advocate setting a target IOP value before surgery, based on the patient's condition and the extent of glaucomatous damage. "For all patients undergoing trabeculectomy, I aim for a low IOP—as close to 10 mm Hg as possible, lower if needed," said Catherine Green, FRANZCO, at the Royal Victorian Eye and Ear Hospital in East Melbourne, Australia.

Dr. Schuman shared his basic guidelines for setting a target IOP. "For patients with severe glaucoma, I might want a pressure of 12 mm Hg or less. If they have moderate glaucoma, 15 to 16 mm Hg might be okay. For early glaucoma, the target IOP might be in the high teens or low 20s."

Warning Signs

After trabeculectomy, frequent monitoring is important. In her practice, Dr. Green follows up with patients on "days 1 and 5 and weekly for the first 4 to 6 weeks—more frequently if there are concerns."

Early resolution. In the early postsurgical period, hypotony may be accompanied by "macular edema and choroidal folds associated with decreased vision, but these consequences often resolve spontaneously," said Dr. Caprioli. However, if they don't resolve, waiting too long to intervene can result in permanent damage. "I usually take action if these consequences of hypotony still are present at 3 or 4 months," he said.

Vision changes. Dr. Caprioli stressed that "regardless of the pressure, the vision has to be monitored very carefully postoperatively. If the visual acuity drops for no other apparent reason," he continued, "it's important to examine the fundus for swelling of the retina, folds in the choroid, or swelling of the optic disc. On slit-lamp exam, you can see if there are changes in the cornea; but typically, changes in the retina are more sensitive to low pressure and precede changes in the cornea." Dr. Schuman stated, "If a person has hypotony maculopathy, I'm going to be aggressive in the intervention because there is a limited time window in which you can restore excellent visual acuity."

Preferred Treatments

In some cases, consequences of hypotony can be managed nonsurgically in the early postoperative period "with atropine and by reducing steroids to try to promote fibrosis," said Dr. Green. However, hypotony maculopathy requires surgical correction.

Revisions. Dr. Green listed her preferences: "transconjunctival suture of the flap, revision of the bleb, or resuturing of the flap." She added, "For the latter, I always have sclera available in case a scleral patch graft is needed." She cautioned that after trabeculectomy, "the sclera can be friable and difficult to handle, especially if MMC has been used." If flow through the ostium cannot be reduced, she recommends applying a patch graft.

Dr. Schuman detailed his process: "You look for a leak, a cyclodialysis cleft, or inflammation to indicate why the pressure is so low. If there's an excellent bleb, then the solution may be limiting the bleb to raise the pressure while staying within the therapeutic window. The first thing I try is compression sutures. If someone has hypotony maculopathy, you might need to be even more aggressive than that." Dr. Schuman noted that, in a case study of recalcitrant hypotony,[6] he and a colleague found that "instillation of perfluorocarbon liquid was successful" in mechanically flattening the retina and choroid and improving vision.

Dr. Caprioli advised, "If the flap is visible, it is often possible to tighten the scleral flap by placing an extra suture transconjunctivally. If you can't see the flap, then the bleb has to be taken down surgically, and the flap has to be tightened directly by adding an extra suture or with tissue patching." In a retrospective series of 33 patients with post-trabeculectomy hypotony maculopathy, Dr. Caprioli and colleagues found that surgical revision of the bleb improved best-corrected visual acuity long term in 29 (88%) of them.[7]

Tips for Trabeculectomy

Can a patient's risk for problematic trabeculectomy-induced hypotony be predicted, and can this outcome be avoided? "Surgeons who perform trabeculectomy generally agree on several risk factors for hypotony maculopathy: younger age, myopia, and a history of vitrectomy," explained Dr. Caprioli. "These factors all are related to the rigidity of the sclera. If the sclera is very compliant and soft, it's more likely to collapse and fold at a lower pressure, which we think is probably one of the causes of hypotony maculopathy." He added, "What we teach—based on collective experience—is that if you have a young myopic male, he is at higher risk for hypotony maculopathy at relatively higher pressures."

Avoid leaks. Dr. Green and her colleagues recently completed an International Council of Ophthalmology Surgical Competency Assessment Rubric (ICO-OSCAR) in trabeculectomy.[8] She said that "good conjunctival closure is essential to prevent wound leak, which would likely cause early hypotony and would require much earlier intervention." Dr. Green explained, "Placement of flap sutures is what determines aqueous flow and is the main determinant of hypotony risk. Sutures need to be tight enough to result in minimal flow at time of surgery."

Titrate the flow. Dr. Caprioli shared his tips for achieving a low target IOP in trabeculectomy: "I place extra sutures or sutures that are a little tight to start with and may yield an IOP that's a little higher than the target. Then in the first few weeks, I selectively cut the sutures in the office with a laser to release tension on the flap and let more fluid through, thereby lowering the IOP to target."

Manage expectations. In certain subgroups of patients, such as those with uveitic glaucoma, detrimental hypotony can be common. Dr. Green and colleagues recently conducted a review of uveitic glaucoma management[9] and found hypotony to be the most common complication of trabeculectomy or glaucoma device implanta-

tion, affecting approximately 30% of patients. She pointed out, "In patients with active uveitis, there is a higher risk of bleb failure, so there is a tendency to use a higher dose of MMC, but this may increase the risk of hypotony."

For particularly high-risk patients, Dr. Green emphasized the importance of preoperative discussions with the patient as part of the consent process: "Managing hypotony can be challenging for both surgeon and patient, so having this understood makes the process slightly easier if it does occur."

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Dr. Caprioli is an ophthalmologist at the Ronald Reagan UCLA Medical Center and is professor of ophthalmology, University of California, Los Angeles. *Financial disclosures: None.*
Dr. Green is an ophthalmologist and Head of the Glaucoma Unit, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia. *Financial disclosures: Allergan: C,L.*
Dr. Schuman is an ophthalmologist at NYU Eye Center, NYU Langone Health, and is a professor of ophthalmology at New York University School of Medicine. *Financial disclosures: Aerie Pharmaceuticals: C; BrightFocus Foundation: S; Carl Zeiss Meditec: P; Department of Defense: S; National Eye Institute: S; Ocugenix: O,P; Ocular Therapeutix: C,S; Opticient: C,O; Slack: C.*

See disclosure key, *page 10.*

EXTRA **MORE ONLINE.** Ruth D. Williams, MD, interviews Anne Louise Coleman, MD, PhD, about ocular hypotony at aao.org/interview/ocular-hypotony.

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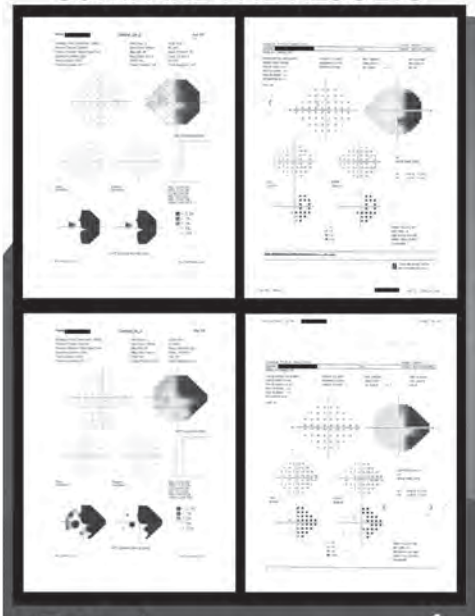

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Prescribing Pediatric Spectacles: More Than Meets the Eye

More than a decade ago, Sean P. Donahue, MD, PhD, at Vanderbilt University in Nashville, Tennessee, published a study demonstrating that a significant number of children are prescribed glasses unnecessarily.[1]

At the time, Dr. Donahue pointed to the extrapolated national costs of these findings to the tune of $200 million in 2004 dollars. Yet, interestingly, the financial impact only tells half the story. The other half involves quality-of-life issues … for the parents.

"A 2011 study out of the Mayo Clinic in Rochester, Minnesota, reported that spectacle wear in children reduced parental health-related quality-of-life"[2] said Jane C. Edmond, MD, at Dell Medical School at the University of Texas, Austin. "Results from this study, combined with the findings that spectacles may be overprescribed in children, has key implications for both pediatric ophthalmologists and general ophthalmologists who treat children," she said.

When considered together, these 2 studies take on new importance given the recent trend toward reimbursing physicians based on quality of care rather than volume, since not only physical outcomes but quality of life/patient-reported outcomes may gain increasing relevance, she said. (See "Reimbursement and Patient Reported Outcomes" on next page.)

"When prescribing spectacles to children, we are good at asking parents about the quality of their child's vision and compliance with the glasses, but very few practitioners think to ask parents about the impact that spectacle prescription has on the quality of their lives," Dr. Edmond noted. "We should be asking all these questions."

EXAM. *Dr. Donahue does a slit-lamp exam.*

Studying Parental Quality of Life

Jonathan M. Holmes, MD, at the Mayo Clinic in Rochester, Minnesota, who coauthored the 2011 paper, first became interested in quality-of-life metrics when studying strabismus. As a member of the Pediatric Eye Disease Investigative Group (PEDIG), which was planning a study for children with intermittent exotropia, he realized that there were "no good instruments to measure the effects of this condition on the child and parents."

A new survey. Through extensive interviews with children and parents, Dr. Holmes and his group developed the Intermittent Exotropia Questionnaire (IXTQ), a validated instrument for measuring health-related quality of life (HRQOL) in children with intermittent exotropia. Children as young as 5 years can self-report, and parent proxy reporting can be used for children of all ages. The IXTQ also contained a parent self-report, addressing how their child's condition affects the parents themselves.

Kids with refractive error only. "We then decided to study quality of life regarding the use of spectacles alone, taking intermittent exotropia out of the equation," Dr. Holmes explained. "The patients (and parents) we reported in the article were just children who had normal vision with or without glasses."

One of the most striking findings, Dr. Holmes said, is that simply wearing glasses did not appear to affect the quality of life in these children (granted, the questionnaire was originally designed for children with intermittent exotropia). The researchers found no differences in composite HRQOL scores for children who wore spectacles and those who did not.

BY LORI BAKER-SCHENA, MBA, EDD, CONTRIBUTING WRITER, INTERVIEWING **SEAN P. DONAHUE, MD, PHD, JANE C. EDMOND, MD, JONATHAN M. HOLMES, MD,** AND **MICHAEL X. REPKA, MD, MBA.**

Sean P. Donahue, MD, PhD

QOL for moms and dads. In contrast, assessment of parental HRQOL using the IXTQ showed that parents of children who wore spectacles had worse HRQOL than those of children who did not wear spectacles. The lower scoring survey questions were related to worry about permanent damage to their child's eyes, long-term eyesight, potential surgery, self-consciousness, and teasing related to wearing glasses.

"We did not anticipate this level of worry among parents," Dr. Holmes noted. "For example, one of the striking differences between parents and children involved teasing. While children with glasses did not perceive that they were being teased, the parents of children with glasses worried that their children would be teased."

Pearls. Dr. Holmes said the clinical pearls from these findings are twofold. First, when prescribing glasses for children, eye care practitioners should acknowledge the potential parental concerns and be sensitive to those concerns in terms of explaining and counseling.

He said, "Our study gave us insight into why parents are upset when their children are prescribed glasses." If clinicians understand what is going on in the parents' minds, they will be better equipped to help dispel worry.

"Secondly, we certainly don't want to unnecessarily prescribe glasses to children who don't need them," Dr. Holmes said. "We need further research on how refractive error affects children and what levels of refractive error need to be corrected. We also need to look at how the correction of refractive error affects the development of eye conditions as the child gets older."

More Than a Decade of Clinical Observations

Dr. Donahue's original interest in quantifying the prevalence of visually normal children wearing glasses stemmed from anecdotal experiences with colleagues over the years. In his 2004 study, he found that nearly 20% of children with normal vision received a prescription for glasses following a visit to an eye doctor, despite not being at risk for amblyopia or another pathology.

"Since we published these findings, we have found that the anecdotal observations have not changed, although we do not have research data to support these anecdotal findings," Dr. Donahue said.

"However, it is important to note that if the child really needs glasses, he or she will most often wear them," Dr. Donahue added. "If the parents are having a hard time getting their child to wear glasses, which will definitely impact their quality of life, then they may want to consider whether the child, in fact, needs the spectacles."

When kids need glasses. Dr. Edmond said that there are situations where not wearing glasses may lead to amblyopia, such as bilateral high hyperopia or anisometropia, which can result in permanent vision loss if untreated at a young age. "In these cases, parents should be advised that the child can experience permanent vision loss" if he or she doesn't comply with the glasses prescription.

When they don't. However, she said, "For a vast majority of children, not wearing their glasses will have no lasting side effect to their visual pathways. The myopic middle or high-schooler may not see well and may have to squint to see the board in the classroom, which could lead to academic issues, but there is no lasting sequelae. And parents should know this."

1 D error? Consider no glasses. Dr. Donahue said his research also showed while spectacles were often prescribed for children having less than 1 D of refractive error, pediatric ophthalmologists were much less likely to prescribe spectacles in such situations.

"General ophthalmologists who see an occasional pediatric patient need to be alert to the fact that the accommodative facility of young children is quite different from [that of] older patients," Dr. Donahue said. "Where a child can focus through large amounts of far sightedness, most of the adult population would be horribly incapacitated by the same amount of refractive error."

Consequently, he advised, it would be worthwhile for general ophthalmologists seeing pediatric patients to be familiar with and implement the Academy *Preferred Practice Patterns* (*PPP*)[3] regarding the management of these children. (Download the *Pediatric Eye Evaluations PPP* at aao.org/ppp.)

Reimbursement and Patient Reported Outcomes

Dr. Edmond noted that her medical school is one of the few centers in the country focusing on value-based health care strategies.

"This is one of the reasons the quality-of-life issue for parents captured my attention," she said. "Increased value in health care means improved outcomes, particularly outcomes that matter to patients and, in this case, the parents. Reimbursements will be increasingly linked to value. We need to start paying attention to this aspect of health care delivery."

Michael X. Repka, MD, MBA, at the Wilmer Eye Institute in Baltimore and serving as Academy Medical Director for Governmental Affairs, said that while quality-of-life measurements are not currently impacting fee-for-service payments to physicians, they may be indirectly affecting other payments. For example, hospitals and outpatient facilities have long been judged on patient satisfaction survey results.

"My institution looks carefully at quality ratings," said Dr. Repka, "and these ratings will probably affect clinical bonuses if poor quality adversely impacts payer payments. At this point, parental quality-of-life survey data for eyeglasses hasn't affected reimbursements. But bonus payments for value may be coming."

Dr. Repka added that if this shift does take place, instruments must be developed to measure patient feedback accurately for specific conditions and provide the detail necessary for the findings to be useful.

Future Research

Dr. Holmes agreed that patient and family perspectives are now increasingly recognized as an important consideration, adding, "I think that our entire field needs better instruments, including more rigorously designed questionnaires that both practitioners and researchers can use in evaluating

the effects of our treatment."

To that end, Dr. Holmes and his team at the Mayo Clinic have been focusing on creating quality-of-life questionnaires for pediatric ophthalmic conditions. In studying children with esotropia and their parents, for example, they identified a wide range of quality-of-life issues from their interviews.[4] Among the most commonly mentioned parental concerns about treatment were inconvenience and, again, worry about glasses.

"While these initial findings are helpful, they are still disease-specific. We truly need additional studies on the impact of spectacle wear on the child and the family," Dr. Holmes said.

"We also need more evidence of when refractive correction is needed and how it benefits children so we don't overprescribe glasses," he added. "These are key areas of research that deserve our attention."

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Dr. Donahue is Coleman Professor and vice chair for Clinical Affairs, Department of Ophthalmology and Clinical Sciences, Vanderbilt University Medical Center in Nashville, Tenn. *Related financial disclosures: None.*

Dr. Edmond is the inaugural director of the Mitchel and Shannon Wong Eye Institute and chair of the Department of Ophthalmology at Dell Medical School at the University of Texas, Austin. *Related financial disclosures: None.*

Dr. Holmes is the Joseph E. and Rose Marie Green Professor of Visual Sciences and professor of ophthalmology at the Mayo Clinic in Rochester, Minn. *Related financial disclosures: National Institutes of Health: S.*

Dr. Repka is the vice chair for Clinical Practice and professor of ophthalmology at the Wilmer Eye Institute in Baltimore. He is also Academy Medical Director for Governmental Affairs. *Related financial disclosures: American Academy of Ophthalmology: C; National Eye Institute: S.*

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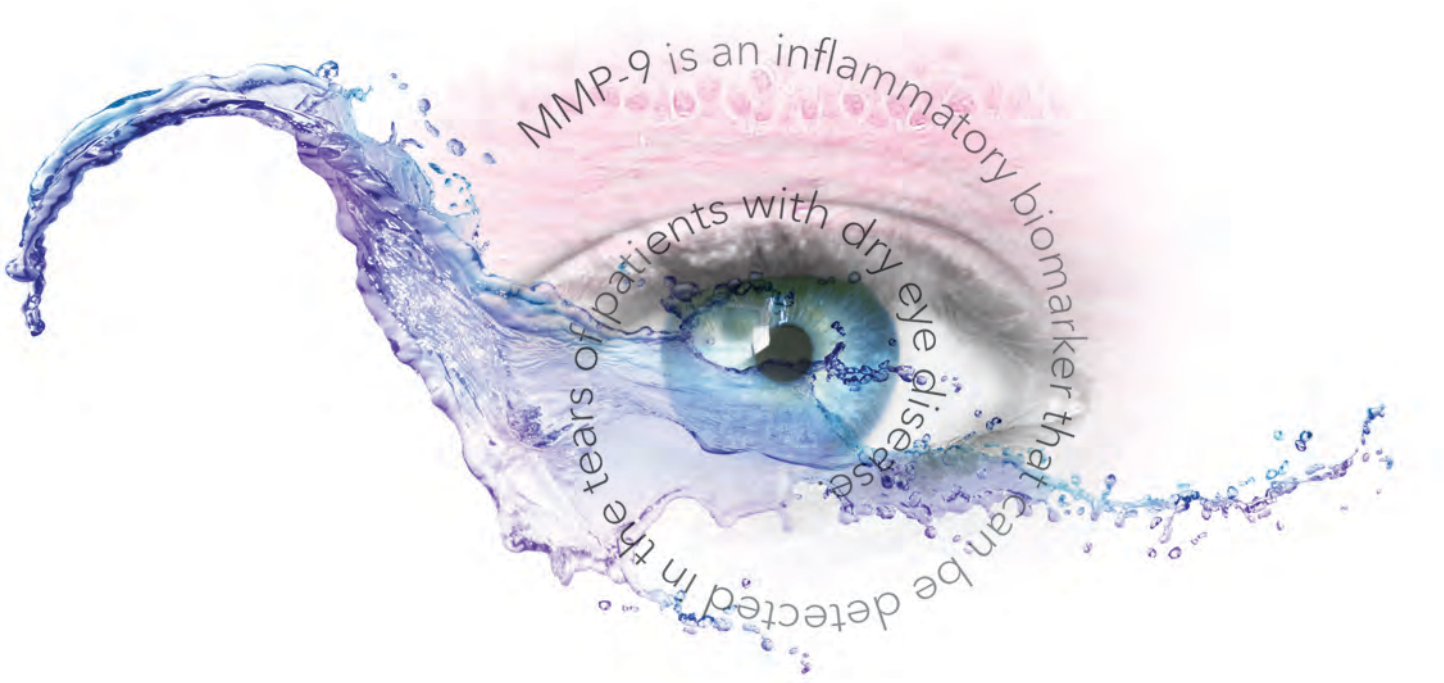

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Management of Proliferative Sickle Cell Retinopathy

Proliferative sickle cell retinopathy (PSR) is a vision-threatening complication of sickle cell disease (SCD). Ischemic events in the retina stimulate angiogenesis, resulting in retinal neovascularization.

SCD is caused by a mutation in the *HBB* gene, which encodes hemoglobin beta. PSR affects up to 40% of heterozygous (HbSC) patients and 20% of homozygous (HbSS) patients.[1] Although most patients remain visually asymptomatic, the incidence of visual loss among patients with HbSS and HbSC affected by PSR has been reported as 31 per 1,000 eyes compared with 1.4 per 1,000 in eyes with nonproliferative disease.[2]

Epidemiology

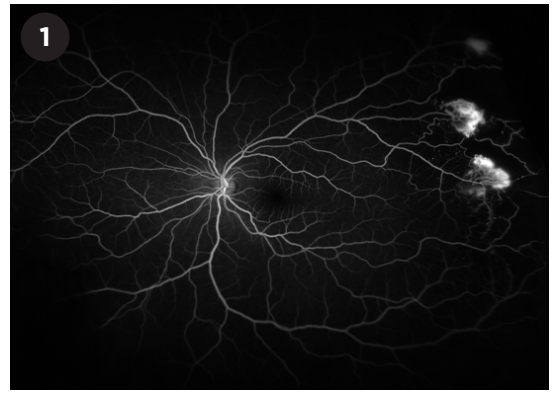
The highest frequency of genotypes associated with HbS is seen in populations of African descent; however, high rates of at-risk genotypes are also seen in people of Mediterranean, Caribbean, South and Central American, Arabic, and East Indian descent.[3]

Patients with the HbSS genotype typically experience greater systemic morbidity, whereas those with the heterozygous genotypes (HbSC and HbS-beta thalassemia) are more likely to manifest PSR. Roughly 32% of HbSC patients will have retinal neovascularization with vitreous hemorrhage compared with 6% of HbSS patients.[4] PSR risk increases with age and is observed more commonly in males. In individuals with HbSC, the peak onset of retinopathy is between 15 and 24 years in men and between 20 and 39 years in women.[5]

Pathophysiology

Red blood cells in patients with SCD are less pliable than normal, resulting in microvascular occlusive events. Subsequent retinal capillary hypoperfusion or nonperfusion and defective oxygen transport lead to local ischemia, which stimulates production of proangiogenic growth factors, such as vascular endothelial growth factor (VEGF), leading to retinal neovascularization. Inflammatory mediators and intracellular adhesion molecules also play an important role in the pathophysiology of PSR.

Retinopathy in HbSC vs. HbSS patients. There are several theories as to why individuals with HbSC genotypes are more likely to develop PSR than those with HbSS. In HbSC, the blood has greater viscosity and higher hematocrit levels, which may lead to small-vessel occlusion in the retinal vasculature.[6] Another theory is that the HbSC state may produce less severe retinal vaso-occlusion, resulting in low-grade chronic ischemia and release of proangiogenic growth factors, thereby creating a more favorable environment for neovascularization.[6] In contrast, individuals with the HbSS phenotype may be less likely to generate an angiogenic response because their vascular occlusion is more complete, producing more profound infarction and leading to retinal necrosis.



SEA FANS. *Ultra-widefield fluorescein angiography demonstrates bright hyperfluorescence of sea-fan neovascularization caused by PSR.*

Retinal Neovascularization

In PSR, the new vessels grow in a frond-like configuration, which has classically been described as resembling a sea fan (Fig. 1). As this sea-fan neovascularization grows along the retinal surface and onto the posterior cortical vitreous, vitreous traction on the neovascular channels may result in intermittent vitreous hemorrhage. Vitreous hemorrhage can also be caused by minor ocular trauma or contraction of vitreous bands from a previous hemorrhage.

Spontaneous regression of the sea-fan neovascularization may occur in up to 60% of patients and is thought to

BY **MASHAL AKHTER, MD, MICHELLE W. LATTING, MD,** AND **ADRIENNE W. SCOTT, MD.** EDITED BY SHARON FEKRAT, MD, AND INGRID U. SCOTT, MD, MPH.

result from autoinfarction.[7]

Sight-threatening complications. In addition to vitreous hemorrhage and vitreoretinal traction, vision-threatening complications of neovascularization include:

- Traction retinal detachment
- Traction retinoschisis
- Macular pucker
- Macular hole
- Retinal break
- Rhegmatogenous or exudative retinal detachment

Course of sea-fan neovascularization. Progression of retinal neovascularization in PSR is variable; some neovascular fronds remain relatively small and flat for many years before autoinfarcting, while others enlarge rapidly and coalesce with neighboring lesions to form larger, elevated, circumferential neovascular complexes.

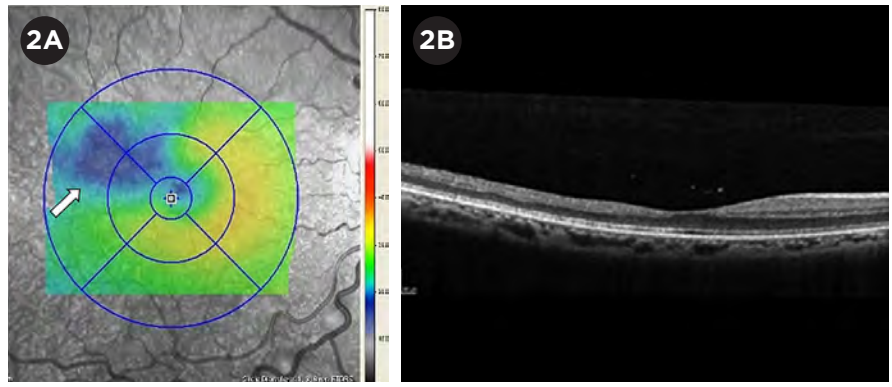
Estimating the age of a PSR lesion is difficult; the clinician is limited to an assessment of the size and degree of elevation above the retinal plane and a semiquantitative assessment of the amount of perfusion and leakage on fluorescein angiography. Disease severity may be quantified by the number of perfused and autoinfarcted sea fans, along with the circumferential extent of PSR.

Screening

Because PSR lesions are typically located in the retinal periphery, individuals with earlier stages of PSR often remain visually asymptomatic. It is recommended that patients with SCD have dilated funduscopic examinations every 1 to 2 years beginning at age 10,[8] preferably by a retina specialist. (These recommendations are based on expert panel consensus, not on large data-driven studies.)

Imaging Modalities

Ultra-widefield imaging (up to 200-degree field of view) is useful in documenting and following PSR lesions. Ultra-widefield fundus photography (UWF-F) and ultra-widefield fluorescein angiography (UWF-FA) have been shown to detect a more-advanced stage of sickle cell retinopathy compared with fundus examination alone.[9] UWF-FA is helpful in showing the extent of leakage from sea-fan lesions and, particularly, in documenting the extent and longitudinal progression of peripheral retinal ischemia (Fig. 1).



FOVEAL FINDINGS. *(2A) SD-OCT demonstrates focal thinning (arrow) within the temporal foveal region in a patient with HbSS disease. (2B) Foveal splaying (saucerization of the foveal pit) is noted in this patient.*

Macular thinning, which increases with age, is common across all genotypes in patients with sickle cell retinopathy.[10] Diffuse thinning may be present throughout the macula, producing a blunted angle of foveal contour, called *foveal splay,* seen on spectral-domain optical coherence tomography (SD-OCT). Focal thinning may also occur in the temporal subfields, a known watershed zone for the macular vasculature (Fig. 2).[11] A recent study showed that SD-OCT in conjunction with complete ophthalmologic examination may lead to earlier detection of retinopathy in children less than 10 years old.[12]

OCT angiography (OCTA) is an emerging imaging modality that can reveal abnormalities in the retinal microvasculature in both proliferative and nonproliferative sickle cell retinopathy. The macular vessel density, specifically in the deep retinal plexus, as seen on OCTA, has been shown to correlate with peripheral nonperfusion seen on UWF-FA in patients with HbSC disease (Fig. 3).[13]

Treatment

Treatment protocols for PSR are not standardized; however, they share the common goal of reducing the risk of progression of neovascular lesions to vitreous hemorrhage and/or retinal detachment.[4] In particular, the aims of therapy are to

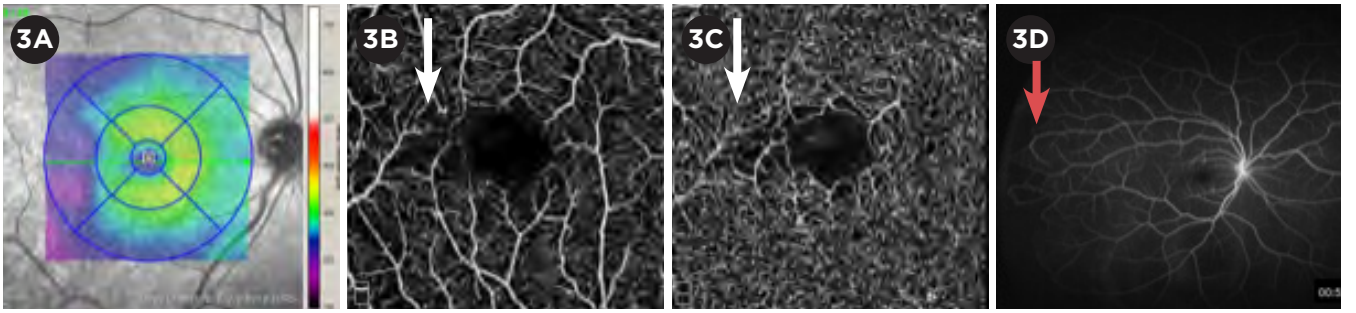
1. Render the lesion avascular and less likely to bleed,
2. Reduce or arrest the chronic transudation of plasma into the vitreous, and
3. Prevent or reduce the vitreoretinal traction that may result from progressive enlargement and forward growth of the lesion into the vitreous.

Treatments that increase fetal hemoglobin, or HbF, such as hydroxyurea, omega-3 fatty acids, and erythropoietin may help to decrease the morbidity of SCD by interfering with the polymerization of HbS and reducing the load of inflammatory mediators.[4] However, it is not yet known how systemic sickle cell status or systemic treatments such as hydroxyurea or exchange transfusions (in which the patient's blood is removed and replaced by a donor's blood) may influence the progression of retinopathy or the development of PSR.

Laser Photocoagulation

Although scatter laser photocoagulation is the current mainstay for managing PSR, there is no evidence-based, widely accepted treatment regimen. Moreover, the published literature is inconclusive on whether retinal laser photocoagulation is effective in changing visual outcomes in PSR.[14]

Patient selection. Laser photocoagulation is generally considered if there is rapid growth or elevation of neovascular lesions, progressive vitreous traction and/or bleeding of a neovascular lesion, or increase in the number of neovascular lesions. This treatment modality may also be considered in cases of ex-



MULTIMODAL VIEWS. *Right eye of HbSS patient shows vascular abnormalities in the macula and the retinal periphery. (3A) Infrared retinal SD-OCT image, with areas of retinal thinning (blue) noted in the outer temporal subfields. (3B) OCTA of the superficial and (3C) deep capillary plexuses with areas of abnormal vascular flow in the temporal juxtafoveal macula (arrows). (3D) UWF-FA shows vascular anastomotic loops in stage 2 PSR (arrow) and temporal nonperfusion in the retinal periphery.*

tensive peripheral nonperfusion, as well as in patients with neovascularization who are likely to have poor adherence to follow-up schedules or those who have visual impairment or blindness in the fellow eye.

Technique. Laser photocoagulation may be performed as local focal treatment to barricade a sea-fan neovascular complex or in a 360-degree circumferential delivery to the peripheral retina (Fig. 4).

Emerging Therapies

Anti-VEGF agents. A single intravitreal injection of anti-VEGF medications such as bevacizumab or ranibizumab may lead to partial regression of sea-fan neovascularization and decreased leakage on fluorescein angiography.[15] The optimal frequency of intravitreal anti-VEGF injections in PSR is unknown; however, evidence suggests that the degree of fibrosis of the sea-fan lesion in response to anti-VEGF therapy may help to determine the schedule of further injections.[15]

Anti-VEGF injection may also be used as an adjunctive therapy for patients with recurrent vitreous hemorrhage who have already received laser treatment. Similar to its use in selected cases of traction retinal detachment and proliferative diabetic retinopathy, bevacizumab has proved helpful in decreasing intraoperative bleeding and dissecting neovascular fronds from the retinal surface when injected prior to vitrectomy.

Surgical Options

Surgery for PSR may be indicated in eyes with retinal detachment, non-clearing vitreous hemorrhage, vitreous hemorrhage that occurs bilaterally or in a monocular patient, macular hole, or symptomatic vitreomacular traction. In all such patients, careful preoperative planning is required, incorporating a multidisciplinary approach with the participation of the vitreoretinal surgery, hematology, and anesthesiology teams.

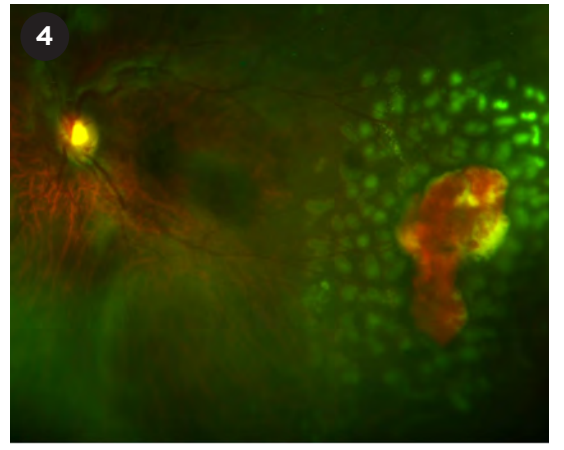
Surgical considerations. General anesthesia is preferred over local, as it allows for optimal intraoperative pain control. If general anesthesia is contraindicated, sub-Tenon's anesthesia is preferred over retrobulbar block, as even modest elevations in intraocular pressure (IOP) may compromise the ophthalmic circulation in sickle cell patients.

Preoperative partial-exchange blood transfusion to increase hemoglobin A to more than 60% should be considered. During surgery, it is important to ensure adequate intraoperative hydration, oxygenation, and careful attention to IOP control. Postoperative exchange transfusion and hospitalization for maximal oxygenation, hydration, and pain management should be considered in patients with SCD.

Vitrectomy. In selected cases of PSR, vitrectomy is indicated in order to achieve clearing of vitreous hemorrhage or to facilitate retinal reattachment.

Retinal traction from neovascular complexes must be relieved. Use of a segmentation technique allows for vertical cutting of the fibrovascular tissue into small sections to relieve circumferential traction. In contrast, delamination involves removing the membranes through horizontal dissection in the plane between the retina and the fibrotic tissue and may be more likely to cause iatrogenic retinal breaks. Sea-fan neovascular complexes are located in the anterior retina, where the tissue is more ischemic and thin and, thus, prone to iatrogenic breaks with even minimal manipulation. Special attention must be paid to management of IOP during vitrectomy, as patients with sickle trait are more prone to vascular occlusions with even modest and transient IOP elevations.

Scleral buckle. Historically, encircling buckles have been relatively



LASER EFFECTS. *A sea-fan lesion with localized hemorrhage is depicted on UWF fundus photography immediately after scatter laser treatment in a patient with HbSC disease.*

(Top) Scott AW et al. Hemoglobinopathies. In: Ryan S et al. *Retina*, 5th ed. Philadelphia: Elsevier Saunders; 2013. (Bottom) Adrienne W. Scott, MD.

contraindicated in patients with SCD, as scleral buckles have been shown to decrease retinal blood flow and alter perfusion of the anterior choroid, ciliary body, and ciliary processes. However, modern, thinner scleral buckles can be used safely in eyes with PSR and may be helpful in supporting areas of peripheral retinal pathology. To avoid anterior segment ischemia in patients with sickle cell status, the surgeon should take care not to place a scleral buckle too tightly.

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Dr. Akhter is a resident at the Kresge Eye Institute, Wayne State University, in Detroit. **Dr. Latting** is a clinical fellow at Bascom Palmer Eye Institute, in Miami. **Dr. Scott** is an associate professor of ophthalmology at the Wilmer Eye Institute, Johns Hopkins University School of Medicine, in Baltimore. *Relevant financial disclosures: None.*

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

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IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

A New Vision

for your patients with an inherited retinal disease (IRD)

LUXTURNA (voretigene neparvovec-rzyl) is a one-time gene therapy that improves functional vision in individuals with an IRD who have confirmed biallelic *RPE65* gene mutations and viable retinal cells.[1]

With LUXTURNA, patients experienced a clinically meaningful improvement in the ability to navigate at lower light levels.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity
Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the following pages.

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

P-RPE65-US-360005 April 2018

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Brief Summary of US Full Prescribing Information for LUXTURNA (voretigene neparvovec-rzyl)

1 INDICATIONS AND USAGE
LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis
Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity
Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities
Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. *[See Dosage and Administration (2.3) in full prescribing information]*

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure
Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles
Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract
Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

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 other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5 x 10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety *[see Clinical Studies (14) in full prescribing information]*. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity
At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary: There is no information regarding the presence of LUXTURNA 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 LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential
No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 *[see Clinical Studies (14) in full prescribing information]* that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use
The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION
Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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The Case of Enigmatic Lid Swelling

Charles Prince* was one of the most upstanding guys you could ever meet. The good-natured, hardworking 53-year-old had a lot on his plate—working a full-time job while caring for his mother, who has Alzheimer disease. He reported that, about 3 weeks earlier, he noticed that his right eye had become red after he lifted his mother. He visited his optometrist, who told him that he had a subconjunctival burst blood vessel.

The redness cleared but returned 2 weeks later. This time it was accompanied by swelling of the right eyelids, which worsened progressively until he couldn't open that eye. He returned to the optometrist, who advised him to go to the nearest emergency department for further evaluation. At that time, Mr. Prince denied ocular pain, pain with eye movements, diplopia, changes in vision, recent trauma, or systemic illnesses, including sinus disease or fevers. He had no other notable medical or ocular history.

We Take a Look

Vital signs revealed that Mr. Prince was afebrile. Uncorrected visual acuity was 20/60 in the right eye and 20/50 in the left eye. Intraocular pressure was 21 mm Hg in the right eye and 11 mm Hg in the left. His pupils were equal, round, and reactive, with no afferent pupillary defect in either eye. Confrontation visual fields, which had to be performed with assistance to raise the right eyelid, were full in both eyes.

Mr. Prince's eyes were straight in primary gaze. The right eye had limitations in all directions of gaze, while the left eye had full ocular movements. Color vision, as tested with Ishihara plates, was normal.

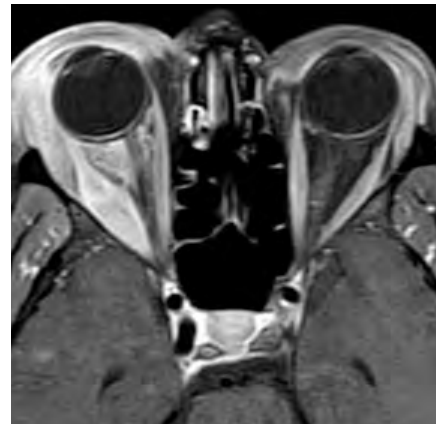
Further exam findings. The right eyelids were firm and edematous, but without erythema or tenderness to palpation. There was trace infraorbital ecchymosis.

Slit-lamp examination showed marked chemosis in the right eye that covered the superior half of the cornea. The remainder of the anterior segment examination, including the entirety of the left eye, was normal.

Funduscopic examination was remarkable only for a few macular drusen bilaterally.

Computed tomography. Maxillofacial CT scan with intravenous (IV) contrast showed diffuse thickening of the skin of the right eyelids, with abnormal contrast enhancement that extended into the orbit and surrounded the globe. The lateral rectus muscle was enlarged. There was no enhancing fluid collection to suggest an abscess, and no active inflammatory process was present in the paranasal sinuses.

Lab results. A complete blood count revealed a hemoglobin level of 9.7 g/dL (normal, 13.5-17.5 g/dL); there was no leukocytosis. Results of a comprehensive metabolic panel were within normal limits.



MRI. *Magnetic resonance imaging shows diffuse inflammation in preseptal and postseptal tissues of the right orbit with thickening of the right lateral rectus muscle.*

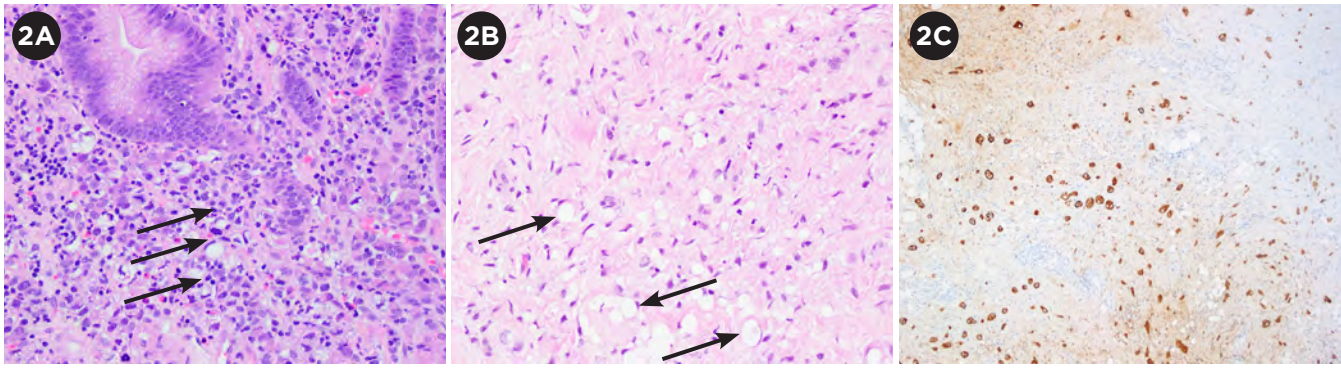
A Tumultuous Hospital Course

Given the extension of contrast enhancement into the orbit, Mr. Prince was admitted to the ophthalmology service with a presumptive diagnosis of orbital cellulitis. He was treated with IV antibiotics, topical erythromycin ophthalmic ointment, and oxymetazoline nasal spray.

Ruling out infection. Inflammatory etiologies were high on our differential diagnosis, but infection needed to be ruled out first. Blood cultures were drawn, and the infectious disease service was consulted.

Mr. Prince remained on IV antibiotics for 3 days, during which time he remained afebrile and pain free. He did not develop leukocytosis, and his blood

BY **APRIL LAO, MD, PRIYA SAHU, MD,** AND **BRUCE BARRON, MD.** EDITED BY STEVEN J. GEDDE, MD.



HISTOPATHOLOGY. *Images from the (2A) gastric biopsy showing signet ring cells, (2B) right eyelid showing poorly differentiated carcinoma with occasional signet cells, and (2C) immunohistochemical staining of the right eyelid tissue, which was positive for pancytokeratin and negative for CD45, CD3, CD20, and S100. Pancytokeratin is found in epithelial cells. The presence of diffuse staining in the biopsy is suggestive of neoplasia.*

cultures were negative for growth. However, his eyelid swelling progressively worsened.

Because of the patient's lack of response to IV antibiotics, we revisited the diagnosis of orbital cellulitis. Orbital inflammatory disease moved to the top of the list of differential diagnoses, and we ordered blood work to evaluate for a possible associated systemic disorder.

Oculoplastics consult. We consulted with the oculoplastics service, which recommended magnetic resonance imaging (MRI) to evaluate for an abscess before starting Mr. Prince on systemic corticosteroids. The MRI showed diffuse inflammation in the preseptal and postseptal tissues of the right orbit; marked thickening and edema of the lateral rectus muscle; and thickening, edema, and enhancement of the lacrimal gland (Fig. 1). There was no active inflammatory process in the paranasal sinuses and no subperiosteal fluid collection or abscess.

Mr. Prince was started on IV methylprednisolone (Solu-Medrol), which he received for 3 days, but the eyelid swelling continued to progress.

Suspicion of malignancy. As the patient's eyelid swelling did not respond to antibiotics or corticosteroids, malignancy rose to the top of our differential. An initial chest x-ray showed soft tissue prominences in the right peritracheal region, right apical region, and right superior mediastinum.

An Unexpected Call

In the middle of a hectic clinic, the resident received a call from the floor that Mr. Prince was vomiting bright red blood. The patient was transferred to the medicine service, the gastrointestinal service was consulted, and an esophagogastroduodenoscopy (EGD) was scheduled for the next day.

As part of the malignancy workup, he also underwent CT scans of the chest, abdomen, and pelvis. These scans showed evidence of bilateral pulmonary emboli; retroperitoneal nodularity and infiltrative tissue that raised concern for lymphoma or another neoplasm; nodular, plaque-like bladder wall thickening; and generalized gastric and focal colonic wall thickening.

EGD revealed 3 ulcers, diffuse edema, and friable tissue throughout the stomach that was strongly suspicious for malignancy. Gastric biopsies were performed, and the eyelid and lacrimal gland were biopsied the following day.

Final Diagnosis

The gastric biopsies revealed invasive poorly differentiated signet ring cell carcinoma. The eyelid biopsies showed poorly differentiated carcinoma, and the lacrimal gland biopsies were suspicious for carcinoma (Fig. 2). Mr. Prince's final diagnosis was signet ring cell gastric carcinoma with widespread metastases, including to the right orbit and eyelids.

Discussion

Orbital metastases. Metastatic involvement of the orbit is uncommon. Orbital metastases occur in 0.07% to 4.7% of patients with malignancies[1] and account for 2% of orbital tumors.[2] Common sites of involvement are the extraocular muscles (because of their rich blood supply) and the bone marrow space of the sphenoid bone (because of its relatively high volume of low-flow blood).[3]

Orbital symptoms and signs, such as pain, proptosis, and ophthalmoplegia, are common. Other signs include blepharoptosis, a palpable mass, blurred vision, and diplopia.[4] The most frequent sources of orbital metastases are the lung, breast, and prostate[4]; gastrointestinal metastases are rare, accounting for approximately 2% of orbital metastases in an Italian study.[5] The presence of orbital metastases is a poor prognostic sign, with an average survival time of 13.5 months after the diagnosis of orbital metastasis.[5]

Eyelid metastases. Eyelid metastases are even rarer, representing 1% of malignant eyelid lesions.[6] There are 3 main patterns of eyelid metastases: nodular, ulcerated, and diffuse. Nodular metastases appear as elevated skin-colored lesions that are sometimes mistaken for chalazia. Ulcerated lesions occur when the malignant cells involve the epidermis. Diffuse lesions present as firm, painless swelling of the periocular skin; they are easily mistaken for contact dermatitis or orbital cellulitis, as in Mr. Prince's case.

Back to Our Patient

At his 1-month oculoplastics follow-up, Mr. Prince was in good spirits and pain free. His ocular examination was stable,

but his visual acuity had decreased to 20/80. Debulking surgery was deferred because he had no evidence of exposure keratopathy or optic nerve compression. He was scheduled to start radiation treatment the next day. Mr. Prince continued palliative radiation treatments but declined palliative chemotherapy.

Over the next several months, he returned 9 times for either gastrointestinal bleeding or shortness of breath from malignant pleural effusions. Four months after his initial presentation, he was admitted to the hospital for profound gastrointestinal bleeding, with a hemoglobin of 5.0 g/dL that required several blood transfusions.

Once stabilized, he underwent EGD, which showed diffuse nodularity of the body, fundus, and antrum of the stomach. There were no discrete lesions that could be cauterized or ligated. Mr. Prince continued to have hematemesis, melena, and hematochezia. After an extensive discussion with his physicians and family, he decided to transition to comfort care. He passed away the next day.

*Patient name is fictitious.

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Dr. Lao is a second-year ophthalmology resident at Louisiana State University Health Sciences Center, New Orleans. **Dr. Sahu** is an oculoplastics specialist at Ochsner Medical Center, New Orleans, and assistant professor of ophthalmology at University of Queensland-Ochsner School of Medicine. **Dr. Barron** is a cornea specialist and clinical professor of ophthalmology at LSU Health Sciences Center, New Orleans. *Financial disclosures: Dr. Barron: Barron Precision Instruments: O.*

See the disclosure key, page 10.

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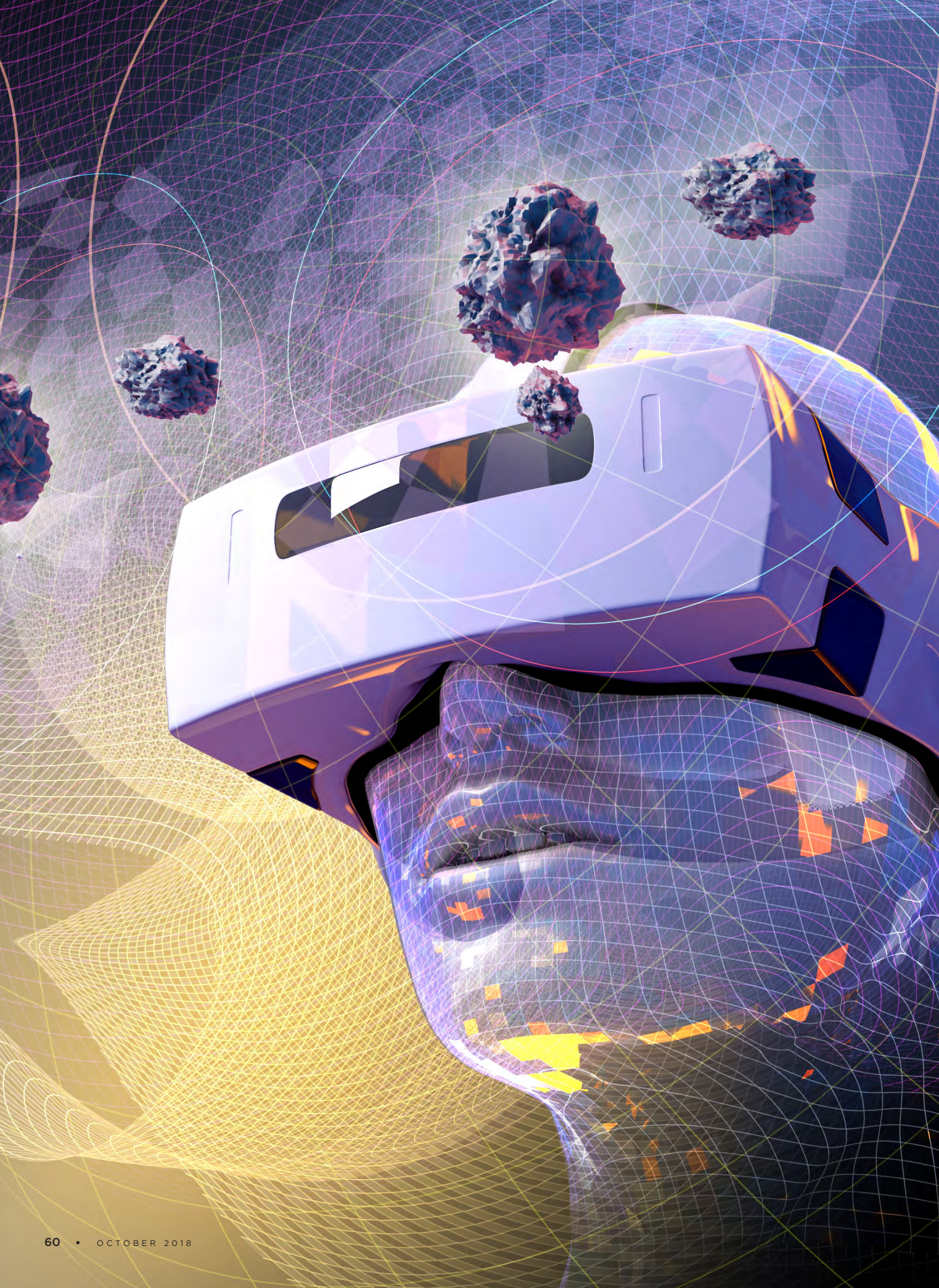


The New World of **Virtual Reality**

Virtual reality technology is showing promise in augmenting traditional assessment and interventional strategies. A look at some lines of investigation.

By Linda Roach, Contributing Writer

VIRTUAL REALITY ISN'T JUST FOR video game buffs anymore. The same technology that fools gamers into believing they are flying an airplane or fighting a medieval battle is moving into multiple areas of medicine.

In ophthalmology, with the exception of education simulators, most of the research into virtual reality (VR) is in the early stages, and these applications have not yet been subjected to rigorous clinical testing. But the work to design and validate them is being carried forward enthusiastically.

Projects in the works include efforts to objectively assess glaucoma; the use of targeted light stimulation to try to rejuvenate failing retinal glanglion cells, and gamelike environments for patients with binocular vision disorders.

Detecting VF Deficits

In the Duke Visual Performance Laboratory directed by glaucoma specialist Felipe A. Medeiros, MD, PhD, researchers hope that their headset—the nGoggle (Ngoggle Diagnostics)—will be the VR tool that establishes a new era in glaucoma management. The goal: a wearable VR system that can detect and quantify visual field (VF) deficits without the subjectivity and inherent imprecision of standard automated perimetry (SAP).

"The idea behind our system was to be able to collect the information about the visual field in an objective way, without relying on subjective patient responses—like having the patient press a button or indicating in some other way that they saw a flash of light," said Dr. Medeiros, at Duke University in Durham, North Carolina.

How it works. The nGoggle integrates wireless electroencephalogram (EEG) and electrooculogram (EOG) sensors, a smartphone-based VR headset, and proprietary software to analyze the information collected. It transmits the data wirelessly to the test administrators. While wearing the headset, the patient passively views patterns of flickering lights on the phone's screen, as the 10 EEG/EOG sensors measure the resulting steady-state visual evoked potentials emanating from the occipital cortex.

Detecting disease progression. Last year, Dr. Medeiros and several colleagues at the University of California, San Diego, reported that the relative levels of these electrical signals could be used to distinguish glaucomatous from normal eyes in a clinic-based setting.[1] Dr. Medeiros has since begun a pilot longitudinal study to investigate whether nGoggle can detect disease progression. If the results are promising, the team hopes to expand the study into a large multicenter clinical trial, he said.

For use at home. "Our main goal is to bring glaucoma patients an evidence-based, portable

device that could be used at home to monitor their visual fields," Dr. Medeiros said. "They could do a lot more tests and do them more often than can be acquired nowadays with the standard visual field testing devices, leading to earlier diagnosis and detection of change. Right now, in the office, the tests are subjective and time-consuming and we can only do them a couple of times per year."

For use in clinical trials? If the pilot trial on disease progression produces positive results, nGoggle also might be a boon to drug companies testing new glaucoma drugs and gene-based treatments for retinal diseases, for example. "There is a clear need for better endpoints that can help expedite clinical trials, allowing quicker, more precise, and more accurate evaluation of the effectiveness of newly proposed therapies," Dr. Medeiros said.

"For some forms of treatment, the FDA is now requiring companies to show that those therapies actually lead to an improvement in an outcome that has real importance to the patient," including quality-of-life outcomes. "[The FDA] is not happy only looking at visual acuity anymore. They want the trials to show, for example, that the new treatment leads to the patient being able to walk better in some type of obstacle course," Dr. Medeiros said. Thus, a VR headset would enable researchers to put subjects through such an obstacle course without exposing them to the risk of falling, he said.

Assessing quality of life. Another goal of Dr. Medeiros's work is to use a variety of virtual reality techniques, including other VR systems and 3-D simulators, to develop a better understanding of how losing vision to an eye disease affects patients' day-to-day lives.

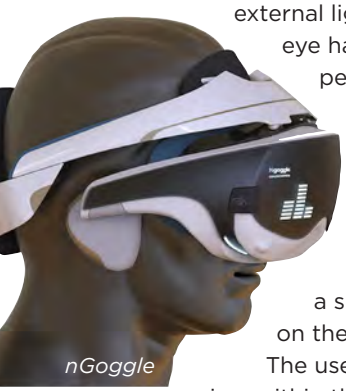
Analyzing risk—and fear—of falling. Dr. Medeiros' group used an Oculus Rift headset (Oculus VR) and a balance platform to demonstrate for the first time that, as glaucoma patients moved through a virtual tunnel, changes in their postural reactivity were indicative of their risk of falling in real life.[2] They also found that patients' postural reactivity to the visual stimulation presented in the VR environment was more closely related to their fear of falling than it was to SAP-measured visual field loss.[3]

REAL-LIFE RISKS. *Dr. Medeiros (shown here with a patient) and his team have used VR to assess glaucoma patients' postural reactivity and fear of falling.*

Evaluating ability to navigate. The researchers

Basics of VR Headsets

Headsets for virtual reality fit like goggles, sealing out external light, and each eye has its own independent view of a display screen. The software controlling the images can reside on a nearby computer, on a smartphone, or on the headset itself. The user rotates the view within the virtual world through head movements and holds a pointer/clicker to move and take actions.



nGoggle

What differentiates one system from another? Some basics to consider:

Tethered. These higher-end headsets must be connected to a gaming system or a desktop computer. Sensors in the headset and an external camera tracker give "6 degrees of freedom" motion tracking (360-degree viewability) within the VR environment. The user holds a game controller, which is also tethered. Popular models include the Oculus Rift and HTC Vive, which sell for roughly $400 and $500, respectively.

Smartphone-based. For this low-cost VR option, a smartphone inserted into the headset frame provides both the viewing screen and the app software to run the VR simulations. One early version was Google Cardboard, which was literally made of cardboard and cost $20 or less; it even could be printed and built at home with online instructions. (Google has since released Daydream View, which sells for under $100.)

Fully mobile. The latest-generation versions require neither a tethered computer nor a smartphone to work. The viewing screen and controlling software are incorporated into the unit, and apps can be downloaded from the Internet. Entry-level models, such as the Pico Goblin and the Oculus Go, sell for under $300.

Ken A. Huth Photography

also used VR visualization screens and 3-D glasses to show that, compared with healthy subjects, people with visual field defects took longer to find their way through a virtual room in which previously visible wayfinding cues had been removed.[4]

"We want to go beyond basic assessment of visual function to more complex visual reality–based tasks that simulate real-world tasks, so that we can better gauge the impact of the disease in patients' lives. The hope is that this will help us determine management strategies to prevent disability, as well as develop new assistive technologies to help those in need," Dr. Medeiros said.

CAPTURING BUBBLES. *In the "Bubbles" game, the player controls a virtual hand to pop the closest bubbles, one after the other. The depth interval between bubbles is controlled by an adaptive staircase procedure. In the default configuration, the 3-D bubble sizes are controlled so that all bubbles have the same image size, which isolates binocular disparity as a cue to depth.*

Augmenting VF Testing

Like Dr. Medeiros, vision scientist Benjamin T. Backus, PhD, is excited about what he sees as the potential for virtual reality to revolutionize and democratize VF testing.

"Visual field testing is to me probably the most exciting application of VR technology in terms of global impact. The Humphrey Visual Field is a fine gold standard, but you can't get a precise enough measurement in a single test to monitor progression and to know whether the person is getting significantly worse within a year," said Dr. Backus, at Vivid Vision, a VR company based in San Francisco.

For use at home. By buying an all-in-one VR headset and loading it with Vivid Vision's software, patients could do multiple VF tests at home and then upload the data to their ophthalmologist and schedule an office visit for conventional testing if the doctor deemed it necessary.

Alternatively, clinicians could invest in a few headsets to loan to patients. "You could send the device home for 2 weeks with every glaucoma patient you have, and they would do the test 10 times over 2 weeks, and the data would be collected over the internet for you to analyze," Dr. Backus said.

Pro: Doesn't require fixation. The Vivid Vision VR software is unique in that it does not require the patient to consciously maintain fixation, he said. "Currently for visual field testing, you have to stare at the same spot for 5 or 10 minutes, and it's difficult for people to do. That's not how the visual system is built," Dr. Backus said. "So [with our VR system], we intentionally have people move their eyes from one moment to the next.

"And we know where they're looking because in the virtual reality environment we built, they have to do a task at fixation, and people naturally put their fovea on that visual target in order to do the task. Then when you flash a stimulus relative to that location you know exactly where it is on the retina," he said.

Con: Limited data. The company intends for its VR-based visual field test to augment, not replace, SAP—and like SAP, the product will not require full FDA approval, Dr. Backus said. Although there is no published research on the testing algorithm, Dr. Backus has presented some of the research at scientific meetings. Last spring, he reported to the Imaging and Perimetry Society meeting in Japan that the VR technique successfully detected angioscotomata.

Other studies are in the works, including a small clinical trial to assess the practicality of the VR system and compare its results to SAP. That study is being conducted at the University of California, San Francisco.

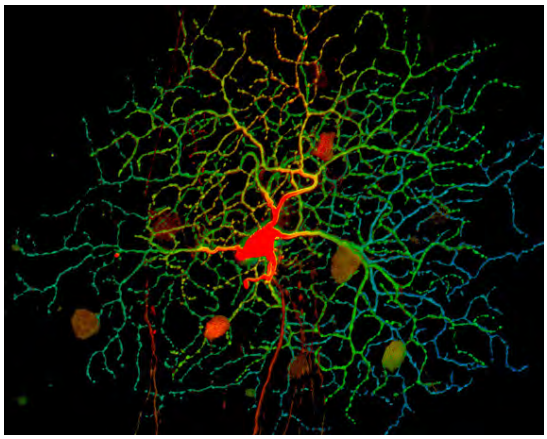
Targeting Axon Regrowth

After demonstrating that visual stimulation could help coax the crushed axons of mouse retinal ganglion cells (RGCs) to regrow and reconnect to the brain,[5] neuroscientist Andrew D. Huberman, PhD, began trying to apply this newfound knowledge to humans—and VR headsets are his tool of choice.

Dr. Huberman, at Stanford University in Palo Alto, California, is in the early stages of testing whether specific forms of pattern visual stimulation, delivered daily with a VR headset, might protect and perhaps regrow RGCs in people with glaucoma. He hopes to report on outcomes at the spring 2019 ARVO meeting.

Since May, the first 2 trial subjects in his pilot

Vivid Vision



RECONNECTION. *One line of research is following the possibility that visual stimulation, delivered by VR, might help protect—and possibly even regrow—retinal ganglion cells (shown here) in people with glaucoma.*

study, ages 17 and 76, have spent 30 minutes a day, 5 days a week, inside a virtual world where customized patterns of white spots are flashed at or adjacent to areas that either are at risk for RGC damage or are already damaged, respectively. The locations are programmed into the wireless headset based on the results of visual field testing and structural measures of retinal health (e.g., optical coherence tomography scans), Dr. Huberman said.

"Some people just need to hold on to the vision they've got. Then, for other people, who have scotomas that are complete and extensive, you would want to deliver the stimulation [in the periscotoma area]." That's because some evidence suggests that, for visual improvement to take place at the level of the cortex, "stimulating central plasticity for the periscotomal region" needs to occur, Dr. Huberman said. In theory, he added, "the recovery in vision could occur through neural regeneration of ganglion cells, or through the filling in of scotomas at the level of the cortex deep in the brain, or both. We really don't know."

Advantages of VR. Dr. Huberman cited the following advantages of VR to his research:

Targeted. The VR headset "allows us to deliver visual stimulation to any location in the eye that we want," he said. Without it, "when you look at something and you move your eyes, the stimulation might not land in the correct place. With VR, we can adjust for that in real time."

Portable. "Patients come in, get their eyes examined and retinas and vision mapped, and then we equip them with wireless headsets that they take home. They can effectively bring the eye clinic home," he said.

Encourages attention. "Another advantage is the ability to vary the stimulation so the patient remains engaged for the 30 minutes per day that we think are required to get ganglion cells to survive better and regenerate," Dr. Huberman said.

Engagement and active attention also are key to the process of neural plasticity, which might factor into trial outcomes, he said. To keep the user's attention, the VR environment in the trial is a virtual art gallery with empty picture frames; after each pattern stimulation is completed successfully, the user is "rewarded" with a picture in the frame.

Improving Binocular Vision

Vivid Vision also is creating content for VR headsets that is aimed at addressing binocular visual function, including stereopsis, oculomotor control, and—perhaps—amblyopia.

The company already is marketing a VR therapy program for binocular vision in both children and adults, which patients can access either in the office of an ophthalmologist or optometrist or at home, after receiving a prescription for home use.

Stereopsis. Virtual reality is well-suited to address lack of binocularity because the content seen through each lens can be carefully controlled, Dr. Backus said. The image in the stronger eye can be displayed in lower contrast or blurred to try to force the 2 eyes to work binocularly (dichoptic stimuli). "Virtual reality lets you take control of the visual input. So you also have complete separation of the left and right eye images. They're generated independently in 2 different displays," he said.

"We did a study in which we had people playing off-the-shelf 3-D video games," said Dennis M. Levi, OD, PhD, who leads a VR testing laboratory at the University of California, Berkeley. Results of the study, conducted in 21 adults, showed improvment in stereo vision.[6]

Amblyopia. Results with amblyopia have been limited so far, Dr. Levi said. In randomized multicenter trials of patching versus a dichoptic game (using red-green glasses to present separate images to the 2 eyes), researchers found no advantage of the video game therapy over patching.[7,8] But those studies used an iPad "falling blocks" game, not an immersive VR game, and the children did not find the game itself compelling enough to play it regularly, Dr. Levi said. "I think we can do much better by using very tailored 3-D or virtual reality games."

Dr. Levi hypothesized that, when given a purposefully designed virtual reality game, children with amblyopia will play the game more often and perhaps will achieve more visual benefit from it than they did in the earlier trials. Vivid Vision is designing a VR game for him to use in this way in a clinical trial, which is set to begin this fall.

National Eye Institute

From Bench to Bedside

VR's availability makes it possible for very recent basic research to move into clinical testing quickly, and with minimal risk to participants, Dr. Huberman said. With regard to his own research on RGCs, he said, "Our study isn't only based on findings from 20 years ago. It is grounded in the latest findings from the neuroscience community, defining what types of stimuli the different kinds of ganglion cells like and how electrical activity of RGCs can influence their survival and regenerative capacity."

Dr. Huberman added, "We feel the patients deserve the best of what's been extracted from the animal studies, in terms of safe clinical trials. We should not be satisfied with continually promising patients that an advance is coming in 5 years, or in 10 years, unless we are also actively moving the research into clinical trials in the fastest way we safely can. I think we—researchers, clinicians, the NIH, and foundations—should all be pushing ourselves to try to shorten that timeline, as long as it can be done in a safe and effective way."

1 Nakanishi M et al. *JAMA Ophthalmol.* 2017;135(6):550-557.
2 Diniz-Filho A et al. *Ophthalmology.* 2015;122(6):1131-1138.
3 Daga FB et al. *PLoS One.* 2017;12(12):e0187220.
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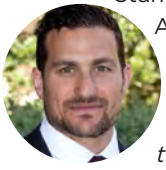
5 Lim JA et al. *Nat Neurosci.* 2016;19(8):1073-1084.
6 Li RW et al. *Ophthalmology.* Published online May 17, 2018.
7 Holmes JM et al. *JAMA Ophthalmol.* 2016;134(12):1391-1400.
8 Manh VM et al., on behalf of the Pediatric Eye Disease Investigator Group. *Am J Ophthalmol.* 2018;186:104-115.

LOOKING AHEAD. For an update on the use of VR in surgical simulation and resident training, watch for the January 2019 issue of *EyeNet*.

MEET THE EXPERTS

Benjamin T. Backus, PhD Chief science officer at Vivid Vision in San Francisco and associate professor in the Graduate Center for Vision Research at the State University of New York College of Optometry in New York City. *Relevant financial disclosures: Research Foundation for SUNY: P; Vivid Vision: O,E.*



Andrew D. Huberman, PhD Associate professor of neurobiology and of ophthalmology at Stanford University School of Medicine in Palo Alto, Calif., and on the affiliated faculty of BioX, Stanford's interdisciplinary biosciences research institute. *Relevant financial disclosures: Glaucoma Research Foundation: S; National Eye Institute: S.*

Dennis M. Levi, OD, PhD Professor of optometry and vision science and immediate past dean of the School of Optometry at the University of California, Berkeley, and a researcher at the university's Helen Wills Neuroscience Institute. *Relevant financial disclosures: None.*

Felipe A. Medeiros, MD, PhD Professor of ophthalmology at Duke University, vice chair for technology and director of clinical research at the Duke Eye Center, and director of the Duke Visual Performance Laboratory, all in Durham, N.C. *Relevant financial disclosures: Carl Zeiss Meditec: C,S; Heidelberg Engineering: C,S; Ngoggle Diagnostics: P; Reichert: S; Topcon: S.*

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

AAO 2018
ART + SCIENCE

MORE AT THE MEETING

Proficiency-Based VR Cataract Surgery for Residents (event code 413). ***When:*** *Monday, Oct. 29, 9-10 a.m.* ***Where:*** *Room S501.* ***Access:*** *Academy Plus course pass.*

Prototyping a 3-D Printed VR Visual Field Analyzer (Po400). ***When:*** *Monday, Oct. 29, 12:45-1:45 p.m.* ***Where:*** *South Hall A.* ***Access:*** *Free.*

Effect of Using a VR Device on Refractive Errors in Children (Po457). ***When:*** *Monday, Oct. 29, 12:45-1:45 p.m.* ***Where:*** *South Hall A.* ***Access:*** *Free.*

A 3-D Visualization Helmet for Vitreoretinal Surgery (Po549). ***When:*** *Monday, Oct. 29, 12:45-1:45 p.m.* ***Where:*** *South Hall A.* ***Access:*** *Free.*

VR Visual Fields and New Algorithms for Visual Field Computer Learning (LL33). ***When:*** *Monday, Oct. 29, 2:30-3:30 p.m.* ***Where:*** *Booth 126, South Hall A.* ***Access:*** *Free.*

INDICATION[1]

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

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

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

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

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

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

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

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

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

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

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

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

AUTOIMMUNITY

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

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

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

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

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

HUMIRA®
adalimumab
destination you™

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

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

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

HUMIRA is proven to[1]:

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

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

*Intermediate, posterior, and panuveitis.

†Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal and/or retinal vascular lesions.

abbvie

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

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

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

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

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

INDICATIONS AND USAGE

Rheumatoid Arthritis

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

Juvenile Idiopathic Arthritis

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

Psoriatic Arthritis

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

Ankylosing Spondylitis

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

Adult Crohn's Disease

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

Pediatric Crohn's Disease

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

Ulcerative Colitis

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

Plaque Psoriasis

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

Hidradenitis Suppurativa

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

Uveitis

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

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

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

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

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

Tuberculosis

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

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

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

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

Monitoring

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

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

Invasive Fungal Infections

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

Malignancies

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

Malignancies in Adults

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

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

Non-Melanoma Skin Cancer

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

Lymphoma and Leukemia

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

Malignancies in Pediatric Patients and Young Adults

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

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

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

Hepatitis B Virus Reactivation

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

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

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

Use with Anakinra

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

Heart Failure

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

Autoimmunity

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

Immunizations

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

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

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

Use with Abatacept

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

Infections

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

Tuberculosis and Opportunistic Infections

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

Autoantibodies

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

Liver Enzyme Elevations

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

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

Immunogenicity

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

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

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

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

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

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

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

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

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

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

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

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

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

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

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

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

Juvenile Idiopathic Arthritis Clinical Studies

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

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

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

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

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

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

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

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

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

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

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

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

Adult Crohn's Disease Clinical Studies

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

Pediatric Crohn's Disease Clinical Studies

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

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

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

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

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

Ulcerative Colitis Clinical Studies

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

Plaque Psoriasis Clinical Studies

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

Hidradenitis Suppurativa Clinical Studies

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

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

Uveitis Clinical Studies

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

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

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

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

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

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

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

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

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

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

Biological Products

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

Live Vaccines

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

Cytochrome P450 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

Clinical Considerations

Fetal/Neonatal adverse reactions

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

Data

Human Data

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

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

Lactation

Risk Summary

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

Pediatric Use

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

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

Juvenile Idiopathic Arthritis

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

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

Pediatric Crohn's Disease

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

Geriatric Use

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

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

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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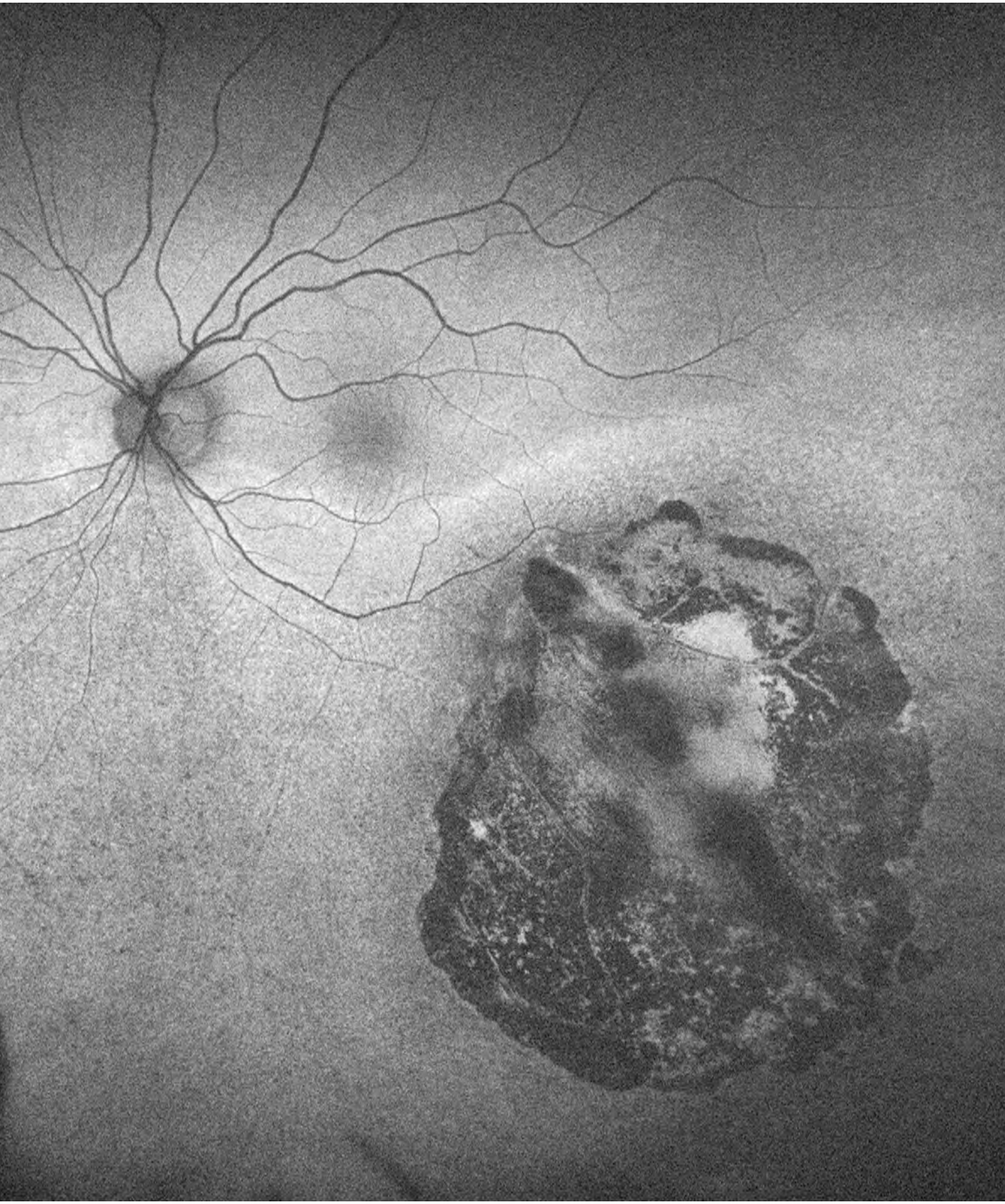


Ultra-Widefield Fundus Autofluorescence Imaging:

An Ophthalmic Photographer's Perspective

Recent technological advances in fundus autofluorescence and the advent of ultra-widefield imaging are providing insights into retinal physiology and pathophysiology.

By Olivia Rainey, OCT-C

Both ultra-widefield (UWF) fundus imaging and fundus autofluorescence (FAF) have significantly improved our understanding of retinal diseases. FAF is useful in determining whether a condition is latent or progressing to healthier areas of the retina, and ultra-widefield fundus autofluorescence (UWF FAF) imaging has provided new opportunities to observe and document changes in the far periphery.

In one study, abnormal FAF patterns were identified outside the central 30 degrees in nearly 70% of patients seen at a tertiary retina clinic; the patients had age-related macular degeneration (AMD), central serous retinopathy, retinal dystrophy, inflammatory disorders, ocular tumors, and retinal vascular disease.[1] Additional research suggests that FAF findings may represent an independent measure of disease stage and activity in early AMD.[2]

A nonmydriatic fundus camera that captures UWF FAF can complement other imaging modalities commonly used in the clinic and can be learned quickly. FAF is noninvasive and produces minimal discomfort in the patient. This allows for efficient and reliable documentation of retinal diseases.

(1) WRONG LATERALITY. *UWF FAF image of the left eye that had the wrong laterality selected when capturing the image, causing the treated choroidal melanoma to become elongated and unreliable for comparison.*

Fundus Autofluorescence

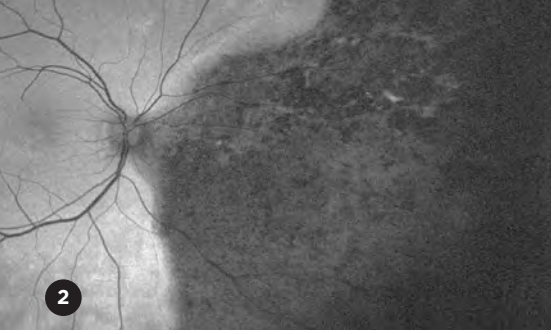
FAF takes advantage of the autofluorescent properties in lipofuscin to identify its absence or accumulation, which can be an indicator of the metabolic state and overall health of the retinal pigment epithelium (RPE).

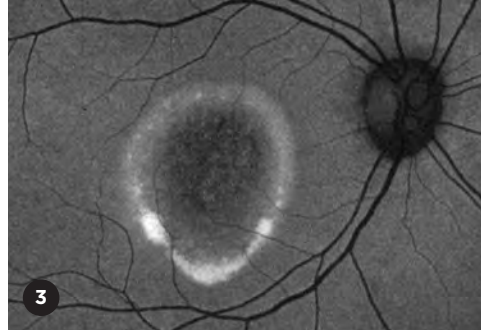
Hypoautofluorescence. Dark areas on FAF typically mean that no lipofuscin is present because the RPE cells have died, indicating vision loss or scotomas (Fig. 2), or that the signal is being absorbed because of interference by blood, pigment, or another blocking artifact. Common findings associated with hypoautofluorescence include RPE atrophy, new hemorrhages, exudative lesions, laser scarring, dense hyperpigmentation, forms of hard drusen, and vitreous opacities.

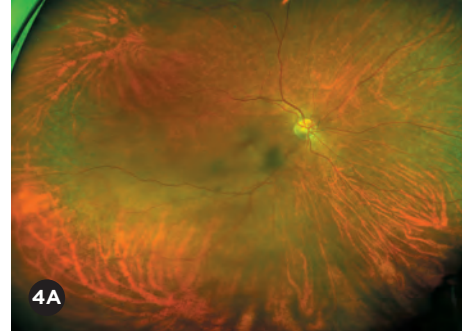
Hyperautofluorescence. Areas that appear hyperautofluorescent, or brighter than the normal gray background autofluorescence, reveal an excess accumulation of lipofuscin and may represent increased metabolic activity of the RPE.

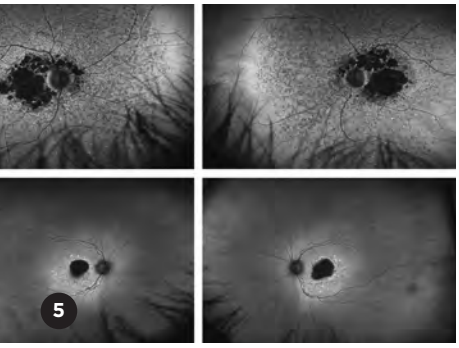
For example, in nonexudative AMD, hyperautofluorescence can surround hypoautofluorescent lesions, which may indicate that these lesions are progressively enlarging; this is often undetectable on fundus examination or other forms of imaging (Fig. 3). Common pathology or characteristics associated with hyperautofluorescence include yellow lesions, bull's-eye maculopathy, older hemorrhages, soft drusen, and demarcation lines.

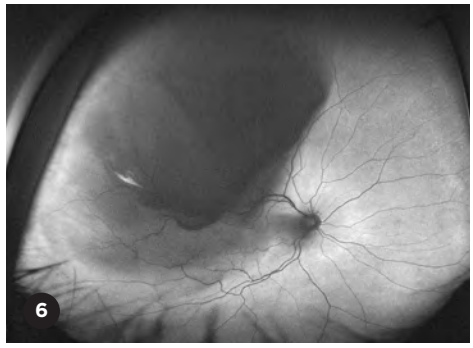
Adapted from Rainey O. *Journal of Ophthalmic Photography.* 2018;40(1):13-21.

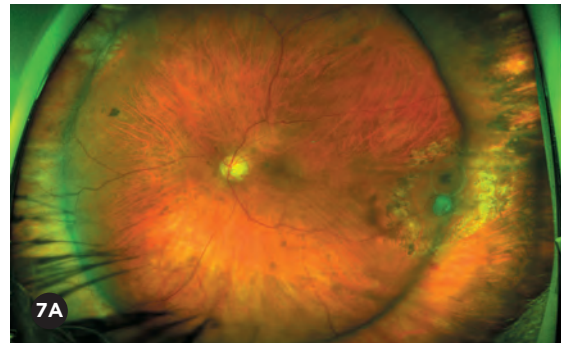












Age-Related Pigmentary Changes

An Age-Related Eye Disease Study on peripheral retinal changes associated with AMD concluded that peripheral retinal changes are more prevalent than previously thought.[3] UWF FAF reveals that there can be significant age-related pigmentary changes in the periphery, and these may look similar to changes that take place in the posterior pole. UWF FAF has shown a loss of melanin granules, peripheral reticular pigmentary changes, cobblestone degeneration, and formation of pseudodrusen in some patients when it may not have been as clearly visible with examination or color fundus photography (Fig. 4).

Inherited Retinal Disease

Because each inherited retinal disease (IRD) can present differently, a physician's ability to recognize the characteristics of each is key to early diagnosis. UWF FAF is particularly helpful in evaluating IRD since the extent of abnormal FAF typically correlates with the results of visual field testing and electroretinography.

The ability to reliably visualize, document, and longitudinally study the extent of IRD has been enhanced through UWF imaging, which can capture most of the periphery for more accurate and complete documentation (Fig. 5).

Retinal Detachment

UWF FAF reveals abnormalities in retinal detachments (RDs) that allow excellent demarcation of the extent of the RDs and assist in both preoperative characterization of the detachment and postoperative counseling.[4] UWF FAF of an RD may reveal hypoautofluorescence in the area of detached retina, which may be due to subretinal fluid blocking the autofluorescent signal (Fig. 6). A leading hyperautofluorescent edge may be present at the margin of the RD. The collection of fluorophores from the photoreceptor outer segments, and/or RPE cells with their increased metabolic activity, may result from the stress at the border of the attached and detached retina (Fig. 7).

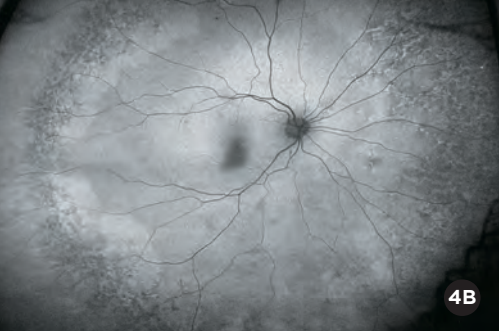
Choroidal Melanoma and Nevus

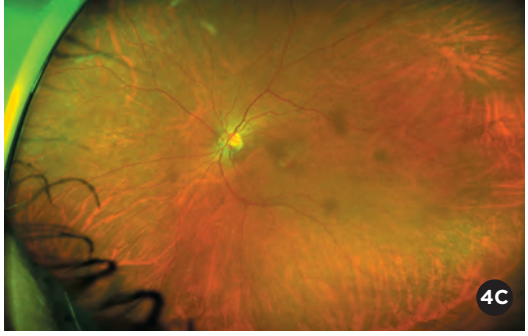
It is common to see abnormal FAF within choroidal melanomas—unlike choroidal nevi, which are less likely to have abnormal FAF. If orange pigment or subretinal fluid is present in choroidal melanoma and nevi, an increase of hyperautofluorescence may be an indication of lesion growth. In large, pigmented choroidal melanomas, there may also be areas of central hypo- or hyperautofluorescence corresponding to RPE atrophy or disruption, respectively.

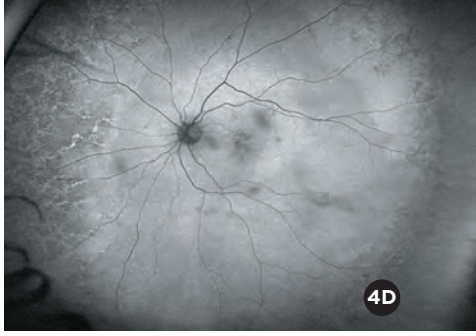
Drawbacks of Diagnosing With UWF FAF: Artifacts

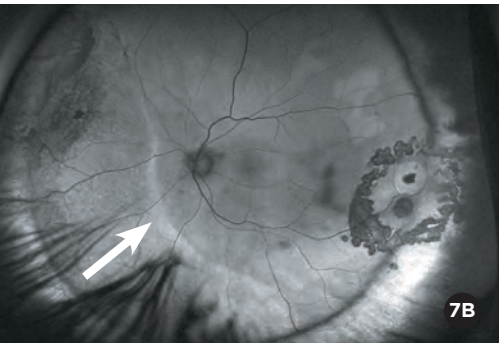
Although UWF FAF is excellent for providing unique insights into many conditions, factors other than the condition itself can affect the clarity and accuracy of UWF FAF images. Should you decide to implement UWF FAF, to be successful, you must be aware that artifacts are possible with any of the UWF systems. FAF imaging is commercially available from companies such as Canon, Heidelberg Engineering, Nidek, Optos, Topcon, and Zeiss. In our clinic, I use the Optos UWF FAF and have observed the following:

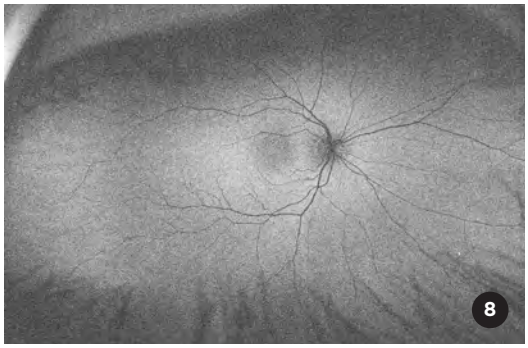
- The physical structures of the eye can block the full view of the periphery. For instance, if patients are not opening their eyes wide enough, if they

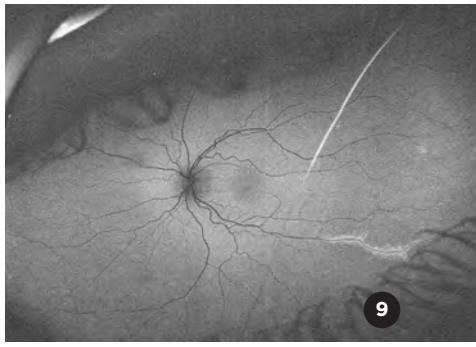












have drooping lids, or if they are light sensitive, the view may be obstructed. I hold patients' eyelids and lashes and instruct them to blink then hold wide before imaging to prevent obscuration of the periphery (Fig. 8).

- The automatic focus usually can get a clear picture. However, significantly elevated lesions may appear slightly blurred. Pathologies within the vitreous can also be difficult to image clearly.
- The shape of the ellipsoid rotating mirror inside the camera can cause distortion of the peripheral fields. In addition, the spherical nature of the globe can make pathology appear elongated and prevent accurate measurement of retinal lesions on the image (Fig. 1).
- Most ophthalmic imaging systems will automatically detect which eye is imaged, yet with the Optos, the technician must select the laterality of the eye; if the wrong eye is selected, the image may appear distorted.
- Various artifacts and opacities such as hair, floaters, haze from inflammation, and hemorrhages can block or interrupt the strong signal necessary for a clear image (Fig. 9).

1 Heussen FM et al. *Invest Ophthalmol Vis Sci.* 2012;53(10):6526-6531.

2 Holz FG et al. Age-related macular degeneration I—early manifestation. In: Holz FG, Schmitz-Valckenberg S, Spaide RF, and Bird AC, eds. *Atlas of Fundus Autofluorescence Imaging.* New York: Springer; 2007:133-147.

3 Domalpally A et al. *Ophthalmology*. 2017;124(4):479-487.

4 Witmer M et al. *Eye* (Lond). 2012;26:1209-1216.

Olivia Rainey, OCT-C, is an ophthalmic photographer at Retina Specialists of Michigan in Grand Rapids. ***Financial disclosures:*** *None.*

(2) LACK OF LIPOFUSCIN. *UWF FAF image of unspecified retinitis of the right eye, revealing a large area of hypoautofluorescence within the periphery.*

(3) LESION ENLARGING. *UWF FAF images of Best disease showing bilateral hyperautofluorescence, with central hypoautofluorescence affecting the macula.*

(4A-4D) UWF FAF ADVANTAGE. *UWF bilateral series of a patient with macular degeneration, showing how UWF FAF reveals significant peripheral reticular changes, whereas in the pseudocolor image, these changes are much less noticeable.*

(5) STARGARDT DISEASE. *UWF FAF bilateral images of Stargardt disease, showing how the same disease can present itself very differently in different patients, yet still have similar characteristics like hypoautofluorescent central lesions with hyperautofluorescent flecks in the periphery.*

(6) RETINAL DETACHMENT. *The UWF FAF image clearly shows the retinal tear in the right eye, causing a macula-off retinal detachment. The superotemporal retina affected by the retinal detachment is very dark and has clearly progressed into the posterior pole.*

(7A, 7B) RD REPAIR. *UWF pseudocolor and UWF FAF images of a retinal detachment repair of the left eye. There is a clear hyperfluorescent leading-edge line within the nasal quadrant of the retina, extending from the inferior to superior retina.*

(8) ARTIFACTS. *UWF FAF image of the right eye with eyelid and eyelash artifact.*

(9) HAIR ARTIFACT. *UWF FAF image with a very noticeable hair artifact in the left eye. However, the peripheral inferior vessel sheathing can still be seen.*

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Premium IOLs—A Legal and Ethical Guide to Billing Medicare Beneficiaries

If you regularly attend the Academy's Codequest meetings, you may have noticed an uptick in questions about out-of-pocket expenses. Here's what you need to know regarding what can and can't be billed out of pocket in conjunction with cataract surgery.

Billing Medicare Patients for the Noncovered Portion

On May 3, 2005, the Centers for Medicare & Medicaid Services (CMS) published a ruling that reversed decades of policy.[1] Previously, services were either covered or not, with no middle ground. Under the 2005 ruling, if a Medicare beneficiary wants a presbyopia-correcting intraocular lens (IOL), Medicare will pay what it would cost to restore functional vision—i.e., the fee for replacing the cataractous lens with a conventional IOL, which is currently $105—and you can bill the patient for additional costs associated with the new lenses.

On Jan. 22, 2007, CMS issued a similar ruling for toric astigmatism-correcting IOLs.[2]

Billing Do's and Don'ts

When a Medicare beneficiary agrees to have a presbyopia- or astigmatic-correcting IOL, rather than a conventional IOL, you need to be careful with your billing.

What *not* to bill Medicare. Under the 2005 and 2007 rulings, Medicare will not cover the following:

- physician services and resources associated with the examination/fitting of premium lenses that exceed coverage for cataract surgery with insertion of a conventional IOL;
- physician services and resources related to refractive examinations specifically associated with insertion of a presbyopia- or astigmatic-correcting IOL;
- subsequent examinations (excluding the 1-time postcataract surgery exam); and
- changes in eyeglasses or lens power needed to accommodate the progression of postoperative presbyopia.

Here's what you can bill to the Medicare beneficiary. You can directly bill the patient for the services and resources that are listed above. You also can bill the patient for the following services:

- Correction of the patient's natural astigmatism with either a blade or a laser. For tracking purposes, practices may create an internal code for this noncovered procedure.
- Optiwave Refractive Analysis (ORA)

BY **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT; **DAVID B. GLASSER, MD,** ACADEMY SECRETARY FOR FEDERAL AFFAIRS; **CHERIE MCNETT,** ACADEMY DIRECTOR OF HEALTH POLICY; **MARA PEARSE BURKE,** ACADEMY ETHICS PROGRAM MANAGER; AND **MICHAEL X. REPKA, MD,** ACADEMY MEDICAL DIRECTOR FOR GOVERNMENTAL AFFAIRS.

Premium Lenses

Presbyiopia-correcting IOLs. HCPCS code V2788 can be used when billing for the IOLs listed below:

- Abbott Medical Optics
  - Tecnis Multifocal 1-Piece (models ZKB00, ZLB00, and ZMB00)
  - Tecnis Multifocal Acrylic (model ZMA00)
  - Tecnis Multifocal Silicone (model ZM900)
- ReZoom
- Alcon
  - AcrySof IQ ReStor (models SN6AD1, SN6AD3, MN6AD1, and SV25T0)
- Bausch + Lomb
  - Crystalens

Astigmatic-correcting IOLs. HCPCS code V2787 can be used when billing for the IOLs listed below:

- Abbott Medical Optics
  - Tecnis Toric 1-Piece (models ZCT150, ZCT225, ZCT300, and ZCT400)
- Alcon
  - AcrySof IQ Toric (models SN6AT3 through SN6AT9; collectively referred to as SN6ATT)
- Bausch + Lomb
  - Trulign Toric (models AT50T, BL1AT, and BL1UT)
- Staar Surgical
  - Silicone 1-Piece Toric (models AA4203TF and AA4203TL)

Note: This list was current at time of press, but new lens models can come on the market at any time.

System Intraoperative Wavefront Aberrometry, but only when a presbyopia- or astigmatic-correcting IOL is implanted and the patient has given his or her consent.

What can ambulatory surgery centers (ASCs) charge? ASCs may bill the patient for the dollar difference between the $105 that Medicare pays for standard cataract surgery and the additional cost of the premium IOL, plus a small handling fee. ASCs may also charge a fee for use of the aberrometer when premium IOLs are used.

What about non-Medicare payers? The CMS rulings for presbyopia- and astigmatic-correcting IOLs apply to Medicare Part B only. Medicare Advantage Plans and commercial plans may have the same coverage, or they may offer more benefits to cover the additional costs. It is imperative that you verify the coverage policy for each individual payer.

Which Codes to Use When Billing for Premium Lenses

Procedure codes. Regardless of what surgical method you use for cataract surgery, you should use CPT code 66984 or, if the surgery qualifies as complex, CPT code 66982. (Note: If you bill the latter code, make sure your documentation clearly indicates what it is that makes the case complex.)

In December 2005, CMS clarified that CPT codes 66985, for a secondary IOL, and 66986, for exchange of an IOL, may be used to report the insertion or replacement of presbyopia- or astigmatic-correcting lenses as well as conventional lenses.[3] However, when using these 2 codes, you can't bill the patient for the extra expense associated with a premium lens.

HCPCS codes. Practices can report the noncovered charges associated with premium IOLs using HCPCS code V2788[3] for a presbyopia-correcting IOL and V2787[4] for an astigmatic-correcting IOL.

However, as a noncovered benefit, physicians are not required to submit these HCPCS codes unless the patient requests that it be submitted.

Furthermore, because you are billing for noncovered service, V2788 and V2787 do not need to have modifier –GY appended to them.

Further Tips

Create a fact sheet. Some practices develop patient information fact sheets that detail the out-of-pocket expenses associated with a premium IOL. Patients can sign this to acknowledge that they understand those costs.

No ABN is needed. Because the premium component of the IOL is statutorily excluded from Medicare coverage, no Advance Beneficiary Notice (ABN) is required.

Medicare patients must be able to opt for the standard IOL. When you are discussing IOL options with cataractous Medicare beneficiaries, you can't tell them that you will only perform surgery if they request a premium lens.

What about additional charges associated with monovision or blended vision? One eye corrected for distance and one eye corrected for near has been an option since aphakic contact lenses were developed. There is no extra allowed billing when conventional IOLs are used.

Femto and Cataract Patients' Best Interests

Protecting patients from unethical practices and acting in their best interests is the primary tenet of the Academy Code of Ethics. Both the Principles and the Rules of the Code address the ophthalmologist's responsibility to act in this way.

When an ophthalmic surgeon has a professionally related commercial interest—such as sole or joint ownership of a femtosecond laser device—the potential exists for a conflict of interest in patient care. It is essential that conflicting commercial interests not interfere with appropriate care.

Femto with a conventional IOL. A surgeon may use a femtosecond laser during cataract surgery when a conventional IOL is implanted (rather than a presbyopia- or astigmatic-correcting IOL), but neither the surgeon nor the facility may obtain additional reimbursement from either Medicare or the Medicare beneficiary over and above the Medicare-allowable amount. Leading patients to believe that you can charge them for this use of the femtosecond laser—for example, via advertisements or in-office financial-aid forms—misrepresents both the services to be performed and the charges made for those services. This misrepresentation limits the patient's autonomy in making appropriate informed decisions for his or her eye care. In the event of an unexpected surgical outcome, the fact of this misrepresentation will weigh heavily against the ophthalmologist if the patient initiates a medicolegal liability action. Charging the patient for this particular use of the femtosecond laser may violate several rules of the Academy's Code of Ethics. The rules concerned with conflict of interest and potential misrepresentation in the above scenario include the following rules: 2. Informed Consent; 9. Medical and Surgical Procedures; 11. Commercial Relationships; 13. Communications to the Public; and 15. Conflict of Interest.

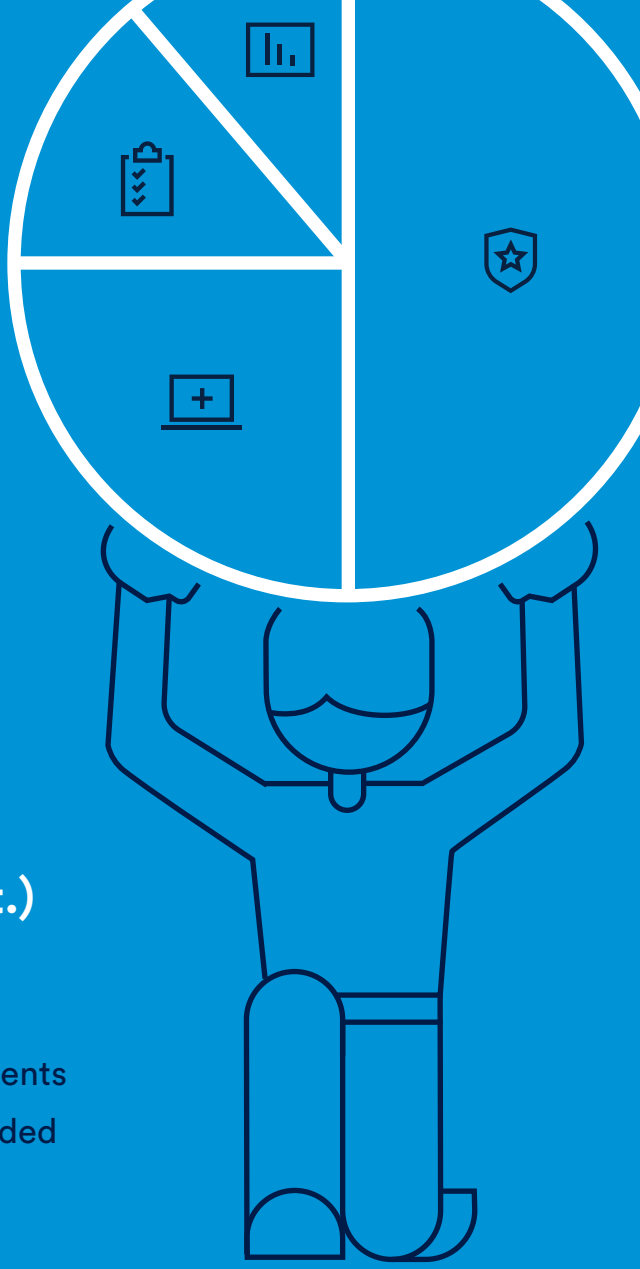
MORE ONLINE. To read the Code of Ethics, visit aao.org/ethics-detail/code-of-ethics. You also can read Guidelines for Billing Medicare Beneficiaries When Using the Femtosecond Laser, published in 2012 by the Academy and the American Society of Cataract and Refractive Surgery. It is available at aao.org/practice-management/coding/updates-resources.

1 CMS Ruling 05-01 May 3, 2005. www.cms.gov/Regulations-and-Guidance/Guidance/Rulings/downloads/CMSR0501.pdf.

2 CMS Ruling 1536-R. Jan. 22, 2007. www.cms.gov/Regulations-and-Guidance/Guidance/Rulings/downloads/CMS1536R.pdf.

3 CMS Transmittal 801. Dec. 30, 2005. www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R801CP.pdf.

4 CMS Transmittal 1430. Feb. 1, 2008. www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R1430CP.pdf.



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How to Use IRIS Registry/EHR Integration to Boost Practice Performance

Why integrate your electronic health record (EHR) system with the IRIS Registry? First, it enables you to compare your performance against that of your peers and identify areas where you can improve patient care. It also provides the least burdensome way to participate in the Merit-Based Incentive Payment System (MIPS), and as a qualified clinical data registry (QCDR), it can offer subspecialty-specific MIPS quality measures that aren't available anywhere else. Furthermore, use of the IRIS Registry is free for U.S. Academy members and their staff.

To help you make the most of IRIS Registry/EHR integration, this article highlights some proven strategies.

4 Practices Share Their Tips

The Academy spoke to 5 IRIS Registry users at 4 U.S. practices about their use of the IRIS Registry. All of them emphasized its convenience and utility for performance monitoring and quality improvement.

Bonnie Allen and Jennifer Laing said that the IRIS Registry dashboard provides an easy, efficient way to monitor practice performance. Ms. Allen is the practice administrator and Ms. Laing is the business office manager at Drs. Fine, Hoffman, and Sims Ophthalmologists, a practice based in Eugene, Oregon, that has 4 providers at 2 sites.

Karen Potts stated that using the IRIS Registry to track performance rates had become second nature at her practice, thanks in no small part to its ease of use. Ms. Potts is the office manager at Koziol-Thoms Eye Associates, a practice in Arlington Heights, Illinois, that has 6 providers.

Michele Huskins added that she runs reports on the group as a whole as well as reports for individual providers. She can print these and hand them to the clinicians, or send them electronically. She works at Rocky Mountain Eye Center, a 19-provider practice in Pueblo, Colorado.

Ufuk Fusun Cardakli, MD, described the IRIS Registry as a tremendous resource that helps her solo practice navigate MIPS. She runs EyeDoc Associates in Altoona, Pennsylvania.

Tip 1: Regularly Review Your IRIS Registry Dashboard

Look at the data monthly. All 5 interviewees urge you to regularly review the IRIS Registry dashboard, which pulls quality metrics directly from a practice's EHR. It shows performance rates on 51 measures, 29 of which can be found only on the IRIS Registry.

Compare your performance against the IRIS Registry benchmarks. Dr. Cardakli noted that she meticulously follows these numbers, looking monthly, as soon as the data are refreshed, comparing her performance to the IRIS Registry benchmarks. She sets a goal of reaching 95%-100% on the quality measures.

IRIS Registry benchmarks differ from MIPS benchmarks. The benchmarks on the IRIS Registry are derived from the current performance of all practices that have integrated their EHR system with it. These differ from the benchmarks that the Centers for Medicare & Medicaid Services (CMS) uses to evaluate performance on MIPS quality measures. For 2018, those CMS benchmarks are based on performance rates of all clinicians who used those measures in 2016.

Break down your practice's performance on a measure. Clinicians can use the dashboard to see how they performed as individuals, how the practice performed as a group, and how the individual- and practice-level performance compares to the average across all physicians in the IRIS Registry.

Tip 2: Communication Is Key

Set up a regular schedule for performance updates. Ms. Allen and Ms. Laing schedule bimonthly executive meetings with physicians and staff. In these meetings, they make sure that scribes and technicians 1) are aware of what needs to be done to meet the requirements of the MIPS quality measures and 2) are getting the information that they need from the physicians to help make sure those requirements are met.

BY MOLLY PELTZMAN, IRIS REGISTRY MANAGER, AND FLORA LUM, MD, ACADEMY VICE PRESIDENT, QUALITY AND DATA SCIENCE DIVISION, INTERVIEWING **BONNIE ALLEN, UFUK FUSUN CARDAKLI, MD, MICHELE HUSKINS, JENNIFER LAING,** AND **KAREN POTTS.**

Don't overwhelm staff. When action is needed, Ms. Potts focuses on 1 quality measure at a time, so staff can focus on making sure any adjustments to procedures are implemented correctly.

Tip 3: Documentation Matters

All 5 interviewees said that the IRIS Registry has helped them identify areas where they need to improve documentation.

Review your performance rate for a measure patient by patient. For example, your performance rate for Measure 18, which appears in the IRIS Registry dashboard as IRIS eCQM 2, is based on the percentage of adult diabetic retinopathy (DR) patients for whom you have documented the presence or absence of macular edema and the level of retinopathy severity. From your dashboard, you can click on this measure to see a list of patients to whom this measure applies (i.e., adults with DR). If your performance rate for this measure is low, you can drill down to see which of those patients are listed as not meeting the measure's requirements.

Next, review their records and determine the source of the problem—perhaps, for example, the documentation was incomplete—and decide how to address that problem in the future. It is possible that the required documentation does exist in the patients' records, but the IRIS Registry isn't mapping your EHR data accurately. If this is the case, you can work with staff at FIGmd, the registry's technical vendor, to improve that data mapping.

Work with FIGmd to identify opportunities to improve documentation. Practices can review their dashboard with their client account representative at FIGmd to see where their measure data are stored within the EHR and the terms or codes used to pull the data. Ms. Huskins, for example, was able to work with FIGmd to review past patient encounters and identify patients who had been wrongly identified as not meeting a measure's requirements. She then worked with the scribes and technicians to take appropriate steps to address those problems.

At her practice, Ms. Potts augmented the EHR system's drop-down menus to include specific keywords and terms that are associated with the quality measure specifications.

Tip 4: You May Need to Make Systematic Changes

Use the dashboard to identify the measures in which your practice is underperforming, and then see if a change in procedures will boost performance.

Identify solutions. To enhance performance on MIPS quality measure 128 (which appears in the dashboard as IRIS14), Ms. Potts' practice added a question on Body Mass Index to the initial patient intake form. For measure 226 (IRIS20), Ms. Huskins included a half-page document in all the exam rooms to remind the technicians to provide patients with information about the effects of smoking on eye health. She also added triggers in her EHR system that prompt users to print such materials. Fixes such as these don't need to add much time but can make a difference across the board.

Use checklists. To ensure consistency in meeting a quality measure's requirements, add checklists to your daily routine. For example, Ms. Potts' checklist includes a reminder to run a report of referrals made by physicians outside the practice. Then staff members call those physician offices to remind them to send their reports to close the referral loop.

Tip 5: Adopt Best Practices

Ms. Allen and Ms. Laing identify the best-performing physician on a measure-by-measure basis. They then determine what is being done differently by that physician (or by his or her clinical staff or scribe) that results

Use the IRIS Registry for MIPS

Join your colleagues. Since it launched in March 2014, the IRIS Registry has proved a popular benefit for U.S. Academy members, with more than 5,000 practices registering to use it for quality improvement and MIPS reporting.

Boost your MIPS score. For performance year 2017, the Academy sent CMS 19,286 sets of data on behalf of IRIS Registry users. Some users had integrated their EHR system with the IRIS Registry; others had entered their MIPS data manually via a web portal. The results speak for themselves:

- all 19,286 submissions avoided the MIPS penalty
- 28% scored 100 points, the maximum MIPS final score
- 85% qualified for the exceptional performance bonus
- 91% of submissions for IRIS Registry/EHR integrated users qualified for the exceptional performance bonus

(Note: These statistics are based on CMS' preliminary scores, which didn't take into account all the nuances of MIPS scoring.)

Report subspecialty-specific QCDR measures that aren't available anywhere else. The IRIS Registry has been designated a qualified clinical data registry (QCDR), which means it is authorized to develop its own measures. Academy staff and committee members have developed subspecialty-specific QCDR measures that capture the true value of medical and surgical eye care. These measures are likely to become increasingly important as the MIPS program focuses more on measures that evaluate outcomes rather than process measures. Importantly, the Academy can modify its QCDR measures annually to account for changes in clinical practice or technology.

Use a reporting mechanism that focuses exclusively on eye care. Changes to the MIPS rules can impact some specialties more than others, which is why Academy experts assess any regulatory changes for their impact on ophthalmology and update the IRIS Registry accordingly.

Haven't signed up for the IRIS Registry? It is too late to register for IRIS Registry/EHR integration this year, but you can still use the IRIS Registry web portal for manual reporting if you register by Nov. 7 at aao.org/iris-registry.

in a higher performance rate. Those best practices can then be implemented across the practice.

Tip 6: Need to Work as a Team

All staff members—from practice administrators and front desk staff to ophthalmologists, optometrists, technicians, and scribes—need to take ownership of improving quality. Everyone needs to be involved with and informed of the practice's quality goals and of what's required to get high performance rates for the measures in the dashboard.

Start early. To encourage high performance, introduce staff to the IRIS Registry dashboard and measures early on in their training. Dr. Cardakli noted that each of her team members knows what is expected for improving quality and understands his or her role in consistently meeting those expectations, whether it's asking patients about their smoking history and noting it in the EHR, prompting Dr. Cardakli to counsel the patient on the benefits of smoking cessation, or—when patients with DR are being seen—identifying the primary care physician who needs to be sent a summary of the visit.

No EHR? No Problem

Practices without an EHR can still use the IRIS Registry for MIPS reporting by manually entering quality measure data and attesting to the improvement activities.

If you report the quality performance category manually, you can choose from 56 measures, including 29 subspecialty-specific QCDR measures that can only be reported via the IRIS Registry.

You also can report the 24 improvement activities that are most meaningful to ophthalmologists.

Register today. If you aren't yet registered to report MIPS manually via the IRIS Registry web portal, you must do so by Nov. 7 at aao.org/iris-registry.

Free Help for Members

FIGmd and IRIS Registry staff are available to answer questions about the IRIS Registry, MIPS quality measures, required documentation, and the MIPS program.

Learn more about the measures found in the IRIS Registry at aao.org/medicare/quality-reporting-measures.

For instructions on how to access your IRIS Registry dashboard, visit aao.org/iris-registry/user-guide/view-performance-reports.

For questions about the IRIS Registry, email irisregistry@aao.org.

For questions about MIPS, email mips@aao.org.

For further reading on MIPS, visit aao.org/medicare and aao.org/eyenet/mips-manual-2018.

AAO 2018 ART + SCIENCE

MORE AT THE MEETING

SATURDAY, OCT. 27

Coding Camp 2 (Event code 18Code2). Enjoy an intermediate-level update on all aspects of coding, including a succinct preview of what to expect from MIPS in 2019. ***When:*** *1:30-4:30 p.m.* ***Where:*** *Room S105a.* ***Access:*** *Separate registration is required.*

SUNDAY, OCT. 28

Government and My Sanity … MACRA, MIPS, HIPAA, and Medicare Advantage (Spe11). Roundtable moderated by Jessica Peterson, MD, MPH, and Joy Woodke. ***When:*** *8:00-9:45 a.m.* ***Where:*** *Room S103b.* ***Access:*** *AAOE members.*

Medicare Forum (Spe20). How is Medicare reimbursement likely to change in 2019? This review will include a MIPS update. ***When:*** *12:15-1:45 p.m.* ***Where:*** *Grand Ballroom S100c.* ***Access:*** *Free.*

The Merit-Based Incentive Payment System (MIPS) in 2019 (251). Sue J. Vicchrilli, COT, OCS, OCS, Jessica Peterson, MD, MPH, and Rebecca Hancock. ***When:*** *3:15-4:15 p.m.* ***Where:*** *Room S105a.* ***Access:*** *Academy Plus course pass.*

MONDAY, OCT. 29

MIPS Promoting Interoperability Panel: Ask Us! (435). Jessica Peterson, MD, MPH. ***When:*** *10:15-11:15 a.m.* ***Where:*** *Room S105b.* ***Access:*** *Academy Plus course pass.*

Government and My Sanity … MACRA, MIPS, HIPAA, and Medicare Advantage (Spe26). Roundtable moderated by Jessica Peterson, MD, MPH, and Joy Woodke. ***When:*** *12:30-1:45 p.m.* ***Where:*** *Room S103b.* ***Access:*** *AAOE members.*

How the IRIS Registry Helps You Participate in MIPS (474). Rebecca Hancock, Joy Woodke, COE, OCS, OCSR, Flora Lum, MD, and Molly Peltzman. ***When:*** *2:00-3:00 p.m.* ***Where:*** *Room S103b.* ***Access:*** *Academy Plus course pass.*

Maximizing PI: Formerly Known as ACI, Previously MU (510). Brittney Wachter, CPC, OCS. ***When:*** *3:15-4:15 p.m.* ***Where:*** *Room S105b.* ***Access:*** *Academy Plus course pass.*

IN THE EXHIBIT HALL

Visit the Academy Resource Center (Booth 508). Bring your MIPS questions to the Coding desk or Advocacy desk. Take your IRIS Registry questions to the IRIS Registry kiosk.

Staff can help you to report your improvement activities. If you are already registered with the IRIS Registry, staff at the IRIS Registry kiosk can help you log in to your account and report on your MIPS improvement activities. If you are able to max out your score for this performance category, that would be enough to avoid the MIPS payment penalty.

To take advantage of this opportunity, make sure you 1) have your IRIS Registry login credentials and 2) know which improvement activities you want to report (aao.org/medicare/improve ment-activities).

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[1] ASCRS Clinical Survey 2015. Global Trends in Ophthalmology and the American Society of Cataract and Refractive Surgery.

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Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Fostering a Diverse Future: Minority Ophthalmology Mentoring

The Academy has launched a brand-new initiative called Minority Ophthalmology Mentoring (MOM). This program is designed to attract underrepresented minorities (African Americans, Hispanics, and Native Americans) to a career in ophthalmology. Through the program, minority students will be encouraged to explore ophthalmology, learn how ophthalmology positively contributes to health care, and discover why ophthalmologists are so passionate about protecting sight and empowering patients' lives. In order to better equip students for medical school and residency, the program offers guidance on students' studies and residency applications, and provides information on research opportunities.

Academy members will serve as mentors for prospective ophthalmologists. In partnership with the Association of University Professors of Ophthalmology, the MOM program matched 25 students—2 undergraduate seniors, 9 first-year medical students, 11 second-year medical students, 2 third-year medical students, and 1 MD/PhD student—with ophthalmologists who will guide them through their education and expose them to the exciting world of ophthalmology.

MOM MENTEE. *Eve Bowers, a second-year medical student, is 1 of 25 student mentees paired with an ophthalmologist mentor as part of the Minority Ophthalmology Mentoring (MOM) program.*

AAO 2018 will provide an exhilarating window into ophthalmology. Mentor-mentee pairs were matched at the end of August, and they meet for the first time in Chicago during the MOM program's Student Engagement Weekend. Throughout this 2-day event at AAO 2018, students will be able to tour the exhibit hall floor, spend time with their mentors, and forge bonds with other mentees. Student Engagement Weekend supports MOM's mission by giving students a comprehensive look at ophthalmology and introducing them to the ophthalmic community fostered by the Academy.

The individual impact. One mentee is Eve Bowers, a second-year medical student at the University of Pittsburgh School of Medicine, who is being mentored by Marcia Carney, MD, current chief of ophthalmology at Fayette Veterans Administration Medical Center (associated with the University of North Carolina Chapel Hill residency training program) and past associate clinical professor of ophthalmology at Virginia Commonwealth University and Eastern Virginia Medical School.

When asked why she wanted to pursue this opportunity, Ms. Bowers said, "I applied to the MOM program because I didn't have relationships with ophthalmologists in Pittsburgh who looked like me, yet I wanted a mentor who understood the particular challenges of being both African American and a woman in eye surgery. The MOM program remains crucial in making the journey to ophthalmology tangible for me and my minority peers by fostering mentorship, visibility, and community."

Her mentor, Dr. Carney, understands the value of mentorship because she, like Ms. Bowers, was once a mentee. Dr. Carney recounted, "My mentor, an African American retina specialist, Dr. Maurice Rabb, along with Dr. Morton Goldberg at the Illinois Eye and Ear Infirmary, trained me as the first African American female vitreoretinal surgeon. The transfer of their knowledge—and their patience—was amazing. Their mission was obvious. They tutored me throughout my tenured career and challenged me to mentor other African American residents of mine with the same fervor. It is an honor and a privilege to emulate their service to teaching and mentoring. We all should be allowed to give back in a way that honors our predecessors and our field."

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For information on mentoring and being mentored, visit aao.org/minority-mentoring.

TAKE NOTICE

MIPS Alert! Don't Miss These Upcoming Deadlines

If you are participating in the Merit-Based Incentive Payment System (MIPS), be sure to note 2 impending deadlines.

By Oct. 3, start your 90-day performance period. This year, you must perform improvement activities and promoting interoperability measures for at least 90 consecutive days. (The performance period for quality measures and cost measures is the full calendar year.)

Make sure you score 100% for improvement activities. All ophthalmologists should be able to max out their score for the improvement activities performance category. Doing that will contribute 15 points to your MIPS final score, which is enough to avoid the MIPS payment penalty.

Reading this after Oct. 3? Your practice may have been performing and documenting improvement activities as a matter of course. For example: IA_EPA_1: *Provide 24/7 access to eligible clinicians or groups who have real-time access to patient's medical record.*

By Nov. 7, sign up for the IRIS Registry web portal. You can use the IRIS Registry (Intelligent Research in Sight) web portal to manually report quality measures, promoting interoperability measures, and improvement activities. This deadline was originally Oct. 31 but has been pushed back to Nov. 7. (Note: If you have already signed up for the IRIS Registry, including for electronic health record integration, you don't need to sign up again for the web portal.)

Your MIPS performance in 2018 affects your payments in 2020. If your MIPS final score is less than 15 points, your payments for Medicare Part B services will be reduced by up to 5% in 2020. Score more than 15 points and those payments will get a small increase; the higher the score, the higher the increase.

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

How to sign up for the IRIS Registry web portal. Visit aao.org/iris-registry and click "Sign up."

Coming to AAO 2018? If you bring your IRIS Registry login credentials, staff at the Academy Resource Center (Booth 508) can help you report your improvement activities and avoid the MIPS payment penalty.

Seeking Outstanding Ophthalmologists

Would you like to nominate a colleague for next year's Outstanding Humanitarian Service Award? The Academy must receive your nomination by March 8, 2019.

This award recognizes Academy fellows and members for outstanding contributions to humanitarian efforts, such as participation in charitable activities, care for the indigent, and community service. It acknowledges those who have performed above and beyond the normal duties of an ophthalmologist.

To obtain a nomination form, contact Member Services by phone, 866-561-8558 (toll-free) or 415-561-8581; by fax, 415-561-8575; or by e-mail, member_services@aao.org. You can also complete a nomination form at aao.org/about/awards/humanitarian.

Submit Your Research to *Ophthalmology*

Ophthalmology, the flagship journal of the Academy, serves the field of ophthalmology as well as the public by publishing clinical science research and other manuscripts that relate to the sense of sight. With an 8.20 Impact Factor and a print circulation of 27,000 subscribers, you can reach a larger audience than ever before. Submit your research today at https://www.evise.com/profile/#/ophtha/login.

Ask the Ethicist: Advertising the "Best" Ophthalmology Practice

Question. Earlier this year, our city's annual business survey ranked our group as the "best" ophthalmic practice in our area. Subsequently, our marketing team printed an advertisement with the quote, "Make your appointment today with the best ophthalmology group in [our area]!" We have received several complaints from colleagues who claim that our ad is unethical and needs to be retracted. Isn't our wording appropriate and ethical because of the survey results?

Answer. Your colleagues are justified in their pique because your ad does not reference the source of the claim. Because of this essential omission, your ad may be interpreted as misleading or untrue.

Your question stimulates a highly relevant discussion: About half of the challenges received by the Academy Ethics Committee focus on ethical advertising. And while the committee does not discourage advertising, we can help guide practices to use it ethically.

Your specific question wrestles with the ethics of claiming superiority. Every claim in an advertisement must be substantiated; failure to substantiate claims carries both ethical and legal ramifications. Section 12 of the Federal Trade Commission (FTC) Act prohibits unsubstantiated claims of superiority. Rule 13 of the Academy Code of Ethics, which addresses advertising and other communications with the public, states, "Communications . . . must not convey false, untrue, deceptive, or misleading information . . . [Ads] must not omit material information without which the communications would be deceptive. [Ads] must not misrepresent an ophthalmologist's . . . experience or ability, and must not contain material claims of superiority that cannot be substantiated."

It can be very difficult to substantiate a claim of superiority, and many ads resort to the use of puffery, or absurd exaggeration (e.g., "the best in the universe"), to sidestep any serious appearance of superiority. You, however, have substantiation for your claim, but

failure to cite the source leaves your advertisement in violation of Rule 13 and the FTC Act.

To be compliant, you must reference the specific survey/poll used to find your practice superior and include dates of the claim. One way to do this would be through footnoting on the printed ad, as with an asterisk. A more prudent way would be to change the wording completely, to a phrase such as: "Voted best ophthalmology practice in [your area] by the [specific survey, with dates]."

For more information, visit The Redmond Ethics Center at aao.org/clinical-education/redmond-ethics-center. To submit a question to the Ethics Committee, email ethics@aao.org.

FOR THE RECORD

Academy Election

The election for open positions on the Board of Trustees begins on Monday, Oct. 29, and closes Tuesday, Nov. 27. Election materials will be sent to all voting Academy fellows and members. Results of the election will be posted on the Academy's website at aao.org/about/governance/elections by Dec. 6, 2018.

CANDIDATES' VIEWS

Anne L. Coleman, MD, PhD

President-Elect

Career. Glaucoma specialist; Fran and Ray Stark Foundation Professor at the Stein Eye Institute at the David Geffen School of Medicine, University of California, Los Angeles; Vice-chair of Academic Affairs for the Department of Ophthalmology; professor of epidemiology at the UCLA Fielding School of Public Health; past President of Women in Ophthalmology; past Council Chair of the American Ophthalmological Society; past Annual Meeting Program Chair for the American Glaucoma Society; past Chair for the National Eye Institute's National Eye Health and Education Planning Committee; 72nd Jackson Memorial Lecturer; member of Research to Prevent Blindness Scientific Advisory Board; associate editor of the *American Journal of Ophthalmology;* member of the National Academy of Medicine.

Dr. Coleman.

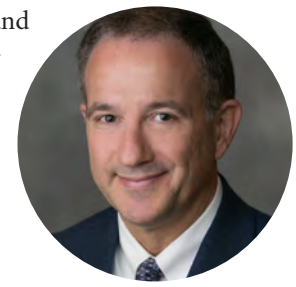
Academy service. Director of H. Dunbar Hoskins Jr., MD, Center for Quality Eye Care; Cochair of David E.I. Pyott Glaucoma Education Center; past Trustee-at-Large; past Quality of Care Secretary.

Goal. To help Academy members achieve our mutual goals to protect and restore sight and empower lives, and to enhance Academy programs for professional and personal improvement.

Christopher J. Rapuano, MD

Senior Secretary for Clinical Education

Academy education experience. Secretary for Lifelong Learning and Assessment for the past 6 years, overseeing many of the Academy's education committees, including the *Basic and Clinical Science Course* (*BCSC*), Resident Education, Ophthalmic Knowledge Assessment Program (OKAP), and Practicing Ophthalmologists Advisory Committee for Education; Chair, Ophthalmic Technology Assessment Committee Refractive Surgery Subcommittee;



Dr. Rapuano.

D.C. REPORT

Advocacy at AAO 2018

In Chicago, several sessions will showcase the Academy's relationship with federal agencies and lawmakers. Take advantage of the Academy's strong advocacy by hearing directly from health policy experts on the issues important to ophthalmology while engaging with your fellow advocates.

"Digital Health & Telemedicine in Ophthalmology" (Spe07). Telemedicine is here, and it's going to reshape your practice and expand your ability to reach patients in every community. This forward-looking session will prepare you for a brave new world in which ophthalmologists offer synchronous and asynchronous care, and in which artificial intelligence is a trusted "member" of your practice. ***When:*** *Saturday, Oct. 27, 12:15-1:45 p.m.* ***Where:*** *Room S103a.* ***Access:*** *Free.*

"Medicare Forum" (Spe20). Every year, Academy experts provide an essential update from Medicare policy's frontlines. When you leave this session, you'll have gained up-to-date guidance on current and future quality initiatives. You'll also understand the Medicare program's evolution beyond fee-for-service. ***When:*** *Sunday, Oct. 28, 12:15-1:45 p.m.* ***Where:*** *Grand Ballroom S100c.* ***Access:*** *Free.*

"Q&A With FDA" (Spe22). Leaders from the U.S. Food and Drug Administration (FDA) will engage directly with you during this popular annual session. Get your drug and device questions answered and hear about the latest regulatory breakthroughs that affect our profession. ***When:*** *Sunday, Oct. 28, 12:45-1:45 p.m.* ***Where:*** *Room S103a.* ***Access:*** *Free.*

"Ocular Trauma Care: The Challenges and Successes in the Continuum of Care for Eye-Injured Service Members and Veterans" (Spe28). Our nation's military are among the first to benefit from breakthroughs in how we treat eye trauma. Hear about the successful efforts to treat our patients in war zones, and consider the challenges we still face as a profession as we continue our care for those who have returned home from service. ***When:*** *Monday, Oct. 29, 12:45-1:45 p.m.* ***Where:*** *Room S103a.* ***Access:*** *Free.*

Chair, *Preferred Practice Patterns* Panel for Cornea; Chair, entire *PPP* Committee; Chair, *BCSC* for Refractive Surgery; Annual Meeting Program Committee for Cornea.

Career. Cornea and refractive surgery specialist at Wills Eye Hospital my entire career; I'm currently the Chief of the Cornea Service. I've taught residents and fellows in clinic and the OR since my first day in practice.

Goal. While the Academy performs a wide variety of extremely valuable functions, I feel strongly that the backbone of the organization is education. My goal is for the Academy to continue to provide the best ophthalmic education in the United States and around the world.

Judy E. Kim, MD
Trustee-at-Large

Career. Graduate of the University of Chicago, Johns Hopkins University School of Medicine, Bascom Palmer Eye Institute of the University of Miami, and the Medical College of Wisconsin (MCW) vitreoretinal fellowship; several years of private practice followed by an academic career; current professor of ophthalmology with tenure at MCW; Director of Teleophthalmology and Research at MCW; leadership experiences include: executive committees of American Society of Retina Specialists and Women in Retina, President of Korean-American Ophthalmology Society and Milwaukee Ophthalmology Society, Commissioner to Joint Commission on Allied Health Personnel in Ophthalmology, Vice-chair of DRCR.net, graduate of the Academy Leadership Development Program XV; recipient of Academy Achievement Award and Senior Achievement Award, and American Society of Retina Specialists' Honor Award and Senior Honor Award.


Dr. Kim.

Academy service. Board Recertification Committee; Lifelong Education for the Ophthalmologist Committee; Special Interest Topics Committee; Current Insight Committee; Retina Subcommittee for EyeWiki; Academy Councilor for American Society of Retina Specialists; Council Regional Meeting Cochair; Awards Committee; Nominating Committee; Subspecialty Section Council Deputy Leader; Retina Subspecialty Day Planning Group.

Goal. To be the voice of our members with integrity and passion and to work with all stakeholders through communication and collaboration. I would be honored to serve you.

ACADEMY RESOURCES

Boost Your Practice Management Skills
The Academy offers a variety of resources to assist you in the business aspects of your practice, such as auditing and patient relations. Check out 2 of the Academy's best resources for practice management learning.

Ophthalmology Business Summit. From March 23-24, 2019, in Chicago, the Academy's second annual business-focused summit will address the key financial and operational challenges that practices are facing right now. For roughly a day and a half, physicians and their senior administrators will team up to gain key insights and actionable strategies that directly impact the revenue and growth of their practices. Take advantage of this rare opportunity to strengthen your practice and exchange knowledge with respected peers in an intimate setting.

For more information, and to register for the event, visit aao.org/business-summit.

The Lean Practice: A Step-By-Step Guide to Running an Efficient and Profitable Ophthalmic Practice. This eBook walks you through a simple yet transformative way to improve your practice efficiency, bottom line, and patient satisfaction. *The Lean Practice* eBook features clear instructions, case studies, downloadable worksheets, and other tools.

Order the eBook at aao.org/store. The eBook is accessible from most computers or on your mobile device through the Academy eBooks app.

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Diamond series ophthalmic lenses

Exceptional optics

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- Low distortion & high resolution
- Superior small pupil performance

Ergonomic, durable design

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Contact lenses: $150.00 *per lens*

Diagnostic lenses

K31-1002
3 mirror*

K31-1005
4 mirror*

Diagnostic & laser lens (PRP)

K31-1330
Retina 200

Bi-aspheric non-contact lenses: $125.00 *per lens*

Diagnostic lenses (slit lamp)

K31-2360
60D

K31-2355
78D

K31-2350
90D

Diagnostic & laser lenses

K31-2370
20D

K31-2365
28D

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The **TRS-5100** offers a split prism Jackson Cross cylinder with simultaneous target comparisons, for faster, more accurate and more positive exam experiences. Maximize exam efficiency, patient flow, and overall practice revenue.

AND DESIRED OUTCOMES

Mitchell A. Jackson, MD
Lake Villa, Illinois

The TRS-5100 rapidly completes all refractions and the split prism allows immediate patient comparison and verification of old vs. new prescriptions – without flipping through lenses and asking "which is better, 1 or 2?"

Larry Patterson, MD
Crossville, TN

The TRS-5100 takes accuracy to a new level and provides the ultimate refraction information that we've been seeking. Now, we have fewer remakes with more satisfied patients who enjoy shorter refraction exam times.

Charles Collins, MD
Middleton, RI

The TRS-5100 is highly valued. It is extremely accurate and I'm very confident in the quality of refraction. It is such a timesaver, has cut down on remakes, reduced our frustrations and increased our bottom line.

Faisal Haq, MD
Plano, Texas

The TRS provides our practice with a diagnostic tool that both improves clinical outcomes while increasing patient flow and overall efficiency. The investment that pays for itself. Wait times are reduced, we see more patients, and we're performing more surgery than ever.

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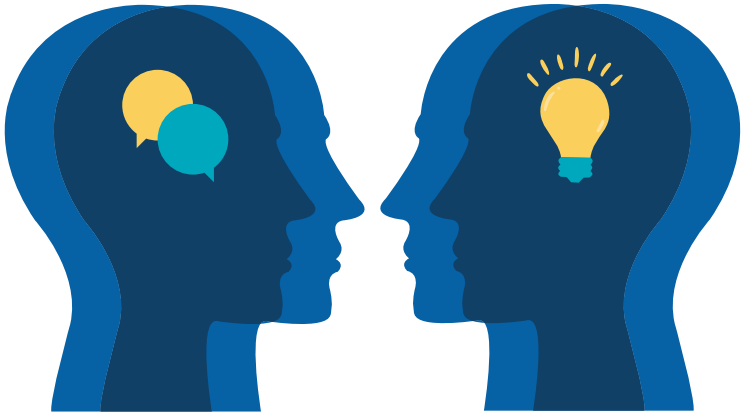
SURGEON TO SURGEON

Saturday, October 27 and Sunday, October 28, 2018

Starting at 10:00 AM and ending at 4:00 PM in the Alcon booth.

REAL solutions begin with REAL conversations.

Be sure to stop by the Alcon booth at AAO to talk one-on-one with surgeons about some of the most innovative eye care technologies in the industry.



Discuss real-world applications of Alcon technologies with experienced surgeons in the following areas:

- Cataract and Refractive Surgery
- Astigmatism Management
- Surgical Retina

REAL SURGEONS REAL ANSWERS

Please visit the Alcon Booth for the full Surgeon to Surgeon schedule. Please note that attendance at these presentations are limited to healthcare professionals. These presentations are not affiliated with the official program of AAO 2018.

All physicians are paid consultants of Alcon.

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Destination AAO 2018

GET READY FOR CHICAGO • PART 6 OF 6

EyeNet thanks Alcon for supporting this year's Destination AAO.

GET YOUR BEARINGS

Register Online—Even in Chicago

Register online for AAO 2018 and purchase tickets and the Academy Plus course pass before and during the meeting by visiting aao.org/registration. You must pick up your badge and/or tickets at the Express Registration–Self Service area in South Hall A. Onsite registration opens Thursday, Oct. 25, at 4:00 p.m.

Before You Fly

The Mobile Meeting Guide (MMG) is the comprehensive reference to the meeting. This mobile site, accessible at aao.org/mobile, offers all program content, including abstracts, handouts, posters, and videos. You can add sessions and events to your calendar, then enable alerts in your MMG settings to have reminders, messages, and announcements texted to you during the meeting. If you need assistance onsite, visit the Tech Bar at the EyePlay Experience, Booth 2581.

When You Arrive

Turning in your bag voucher at the Bags and Programs counter in South Hall A verifies your attendance at AAO 2018. You will also receive your meeting bag, which includes the *Meeting Program,* a condensed guide to AAO 2018 and Subspecialty Day with a fold-out map of the convention center.

MedMeetings Images, Todd Buchanan

AAO 2018 WALKING CHALLENGE. *Sign up for the Academy's first step challenge. Download the challenge app, which will use the data from your step tracking device (e.g., FitBit, Apple Watch, health app on your iPhone) to track your progress against that of your colleagues. Use the app's QR scanner at designated checkpoints around the convention center to earn extra steps. There will be daily prizes, and the 25 attendees who walk the most overall will be entered into a raffle to win 3 grand prizes, including a free hotel room for AAO 2019 in San Francisco. For more information, visit aao.org/step.*

MEETING NEWS

Read *AAO 2018 News*

Every year, *EyeNet* publishes 2 editions of its special meeting tabloid. Look for *AAO 2018 News* in 3 locations: near the escalator on Level 1; next to the bridge in Lakeside; and in the Resource Center, Booth 508.

Subspecialty Day edition (available Friday, Oct. 26, and Saturday, Oct. 27). Read about Subspecialty Day presentations recommended by the program directors. Get tips on touring Chicago from a local. Revisit the year's most popular "Journal Highlights," and hear about the new *Ophthalmology Glaucoma* from Editor-in-Chief Henry D. Jampel, MD. In addition, enjoy award-winning photographs from the Ophthalmic Photographers' Society's 2017 exhibit. Previews of the honorary lectures and information about office ergonomics are also featured.

AAO 2018 edition (available Sunday, Oct. 28, through Tuesday, Oct. 30). Pick up the second edition for an in-depth profile of the 2018 Laureate, Steven

AMERICAN ACADEMY OF OPHTHALMOLOGY®

T. Charles, MD, and read summaries of the Best of Show surgical videos. Other highlights include profiles of the Academy President's Guests of Honor, the best "Blink" mysteries of the year, and an inside look at the Museum of Vision's exhibit on Renaissance and early modern ophthalmic medicine.

Check Your Email for AAO 2018 Daily

For summaries of clinical highlights from Subspecialty Day and the annual meeting, read AAO 2018 Daily, a brief bulletin emailed each evening from Friday, Oct. 26, through Monday, Oct. 29. AAO 2018 Daily is reported in Chicago, allowing ophthalmologists at the meeting and at home to stay on top of news from Subspecialty Day and AAO 2018. Articles will also be posted at aao.org/eyenet/daily.

EVENTS

Connect With Colleagues

AAO 2018 is about learning from and getting to know your colleagues. Check out the following opportunities to connect during the meeting:

Lounges. Relax and network with peers at the International Lounge, the Senior Ophthalmologist (SO) Lounge, or the Young Ophthalmologist (YO) Lounge—all 3 of which are in the Grand Concourse, Level 3. American Academy of Ophthalmic Executives (AAOE) members can mingle in the AAOE Member Lounge in Room S104b. Admittance is by attendee badge.

Offsite events. During AAO 2018, connect with old friends and meet new colleagues at alumni and related events listed at aao.org/annual-meeting/alumni-events.

Digital. The Mobile Meeting Guide (MMG) has a feature allowing you to message other attendees and session presenters. Thank a lecturer, ask a burning question, reconnect with old friends, or plan lunch with new colleagues by visiting aao.org/mobile.

Enjoy *EyeNet* Corporate Lunches

Leave room in your schedule for *EyeNet*'s free corporate educational lunches from Saturday Oct. 27, through Monday, Oct. 29, 12:30-1:30 p.m. Complimentary boxed meals are available on a first-come basis, with lunch pickup beginning at 12:15 p.m. Topics are as follows:

- Saturday, Oct. 27: "Diabetic Eye Disease: Clinical Challenges and Practical Tips for Multidisciplinary Disease Management," supported by Regeneron Pharmaceuticals.
- Sunday, Oct. 28: "INSiiGHTS AT AAO: A Spotlight on Dry Eye Treatment," supported by Shire.
- Monday, Oct. 29: "Cataract Surgery: Life is Beautiful When the Pupil Behaves," supported by Omeros Corporation.

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

For more information, visit aao.org/eyenet/corporate-events.

Academy Events in the Exhibit Hall

Attend events at the Academy Resource Center and Museum of Vision booths:

Academy Foundation donor reception. Meet Academy leaders, learn about the future home of the Museum of Vision, and enjoy refreshments. ***When:*** *Saturday, Oct. 27, 3:00-5:00 p.m.* ***Where:*** *Museum of Vision, Booth 704.* ***Access:*** *Foundation donors.*

Ophthalmology Glaucoma **and** ***Ophthalmology Retina*** **launch celebration.** Meet Editors-in-Chief Henry D. Jampel, MD, MHS, and Andrew P. Schachat, MD, and the editorial boards. ***When:*** *Sunday, Oct. 28, 10:00-11:00 a.m.* ***Where:*** *Resource Center, Booth 508.* ***Access:*** *Journal reviewers, authors, and subscribers.*

EyeCare America volunteer reception. Calling all EyeCare America volunteer-ophthalmologists and residents who have pledged to volunteer (once they become practicing ophthalmologists) to mingle with seasoned volunteers and enjoy snacks and beverages. Volunteers are encouraged to bring a friend interested in volunteering. Volunteers leave with a recognition gift. ***When:*** *Sunday, Oct. 28, 3:00-4:30 p.m.* ***Where:*** *Museum of Vision, Booth 704.* ***Access:*** *Current and future volunteers.*

2019 ***Focal Points*** **social.** Preview the new *Focal Points* format, which launches January 2019. Each new issue will examine current research and discuss practical implementation. ***When:*** *Monday, Oct. 29, 4:00-5:00 p.m.* ***Where:*** *Resource Center, Booth 508.* ***Access:*** Focal Points *participants and subscribers.*

Orbital Gala Auction

Tickets to the Academy Foundation's Orbital Gala at AAO 2018 are available until Friday, Oct. 19.

This year's silent auction features a variety of items, including an escape to Costa Rica, a Nidek Retinal Functional Analyzer MP-1S (valued at $37,250), front-row Chicago Bulls tickets, a Breckenridge ski getaway, and gift certificates for fine wine. Join the bidding during the Gala Sunday, Oct. 28, 6:00-10:00 p.m.

Unable to attend? U.S. members can use their mobile devices to bid on auction items starting Monday, Oct. 22.

For an auction preview, visit aao.org/auction. **To buy tickets to the gala,** visit aao.org/galatickets.

HALL HIGHLIGHTS

Explore the Exhibition

New Exhibitors. This year's show features the New Exhibitor Pavilion, Booths 2270-2879. This designated area, identified by overhead signs and shaded on the map, allows you to quickly find all the newest industry offerings at AAO 2018.

Hall Preview. To efficiently navigate the exhibit hall, plan your trip by using the Virtual Exhibition, accessible at aao.org/virtual-exhibition. Review exhibitors by company name, booth number, product categories, medical specialties, common equipment terms, and basic ophthalmic conditions. For help onsite, visit the Exhibitor Locator, Booth 3400.

Academy Resource Center

At the Academy Resource Center, you will have the opportunity to:

ACADEMY RESOURCE CENTER. *Visit Booth 508 to explore the Academy's latest product offerings, receive help from IRIS Registry and MIPS experts, and more.*

- get 10% off all products with no minimum purchase required;
- demo the Ophthalmic News and Education (ONE) Network;
- talk to coding experts from the American Academy of Ophthalmic Executives
- learn about the IRIS Registry (Intelligent Research in Sight);
- ask questions about the Merit-Based Incentive Payment System (MIPS);
- get help reporting MIPS improvement activities via the IRIS Registry;
- report your Continuing Medical Education credits;
- hear about the Academy's advocacy at the federal and state levels;
- check on your membership status; and
- donate to the Academy Foundation.

Learning Options in the Exhibit Hall

Take advantage of additional educational opportunities on the exhibit hall floor:

Product Theater Talks. Visit the Technology Pavilion (Booth 168) for refreshments during these Product Theater Talks: Nidek from 9:30-10:30 a.m. and AbbVie from 12:30-1:30 p.m. on Saturday, Oct. 27; Spark Therapeutics from 9:30-10:30 a.m. on Sunday, Oct. 28; and Sun Ophthalmics from 9:30-10:30 a.m. on Monday, Oct. 29. Return to the Technology Pavilion throughout the day for tech-related talks.

Learning Lounge. Pop into Booth 126 throughout the day to participate in small-group discussions and presentations on a variety of topics.

Scientific Posters. View the scientific posters in South Hall A. Posters are on display during 2 sessions.

- Session 1: Saturday, Oct. 27, 9:00 a.m.-5:00 p.m., and Sunday, Oct. 28, 7:00 a.m.-5:00 p.m. Session 1 authors will be at their posters and available to chat Sunday, 12:45-1:45 p.m.
- Session 2: Monday, Oct. 29, 7:00 a.m.-5:00 p.m., and Tuesday, Oct. 30, 7:00 a.m.-1:00 p.m. Authors will be at their posters Monday, 12:45-1:45 p.m.

This is the last year that hard-copy posters will be on display. Starting in 2019, posters will only be electronic. As always, posters are also accessible through the Mobile Meeting Guide (MMG).

Visit the Scientific Poster Theater. Attend small-group, peer-moderated discussions of selected posters in the Scientific Poster Theater (South Hall A). Each session will focus on a subspecialty. Sessions are free with your AAO 2018 registration.

For a schedule of these events, view your copy of the *Meeting Program,* or access the MMG at aao.org/mobile.

Check Out the EyePlay Experience

Take a break at the EyePlay booth and give back to the community, recharge your mobile device in the new Charging Lounge, relieve stress with therapy animals, challenge a colleague to Ping-Pong, take a selfie with a giant #aao2018 hashtag, enjoy a complimentary seated massage, get assistance at the Tech Bar, or just hang out.

When: *Saturday, Oct. 27, through Monday, Oct. 29, 9:00 a.m.-5:00 p.m., and Tuesday, Oct. 30, 9:00 a.m.-1:00 p.m.* ***Where:*** *Booth 2581.* ***Access:*** *Free. (Note: Some activities, such as visiting therapy animals, are during set times; for a schedule, check the Mobile Meeting Guide at aao.org/mobile.)*

PROGRAM

Virtual Meeting

The AAO Virtual Meeting is a free online component of AAO 2018 that allows you to access approximately 20 hours of content streamed live from Friday, Oct. 26, through Tuesday, Oct. 30. You will then be able to access archived sessions until Thursday, Jan. 31, 2019.

View the schedule and sign up to participate at aao.org/virtual-meeting.

Sym55: The Value of IRIS Registry

Over 18,000 physicians are participating in the IRIS Registry (Intelligent Research in Sight) to improve quality of care and patient outcomes, as well as to meet federal reporting requirements under Medicare. The IRIS Registry is now the largest specialty clinical data registry in the world, and with all of the information it has collected, the IRIS Registry is supporting research to inform clinical knowledge and support scientific discoveries.

Attend the IRIS symposium entitled "The Value of IRIS Registry: What Can We Learn From 250 Million Patient Records?" (Sym55) to find out about some of the Registry's research currently underway and insights that have already been gleaned from Registry data. ***When:*** *Sunday, Oct. 28, 12:45-1:45 p.m.* ***Where:*** *Room E350.* ***Access:*** *Free.*

Hot Practice Management Courses

From the front office to the exam room, the AAO 2018 program tackles a wide range of practice management topics.

Attend an instruction course. Highlights include the following:

- "The Merit-Based Incentive Payment System (MIPS) in 2019" (251). ***When:*** *Sunday, Oct. 28, 3:15-4:15 p.m.* ***Where:*** *Room S105.* ***Access:*** *Academy*

Plus course pass.

- "Private Equity and Other Equity Transfers: What's My Practice Worth?" (261). ***When:*** *Sunday, Oct. 28, 3:15-5:30 p.m.* ***Where:*** *Room S105d.* ***Access:*** *Academy Plus course pass.*
- "Surviving the Epidemic of Intravitreal Injections" (439). ***When:*** *Monday, Oct. 29, 10:15-11:15 a.m.* ***Where:*** *Room S103bc.* ***Access:*** *Academy Plus course pass.*
- "How the IRIS Registry Helps You Participate in MIPS" (474). ***When:*** *Monday, Oct. 29, 2:00-3:00 p.m.* ***Where:*** *Room S103bc.* ***Access:*** *Academy Plus course pass.*
- "Maximizing PI: Formerly Known as ACI, Previously MU" (510). ***When:*** *Monday, Oct. 29, 3:15-4:15 p.m.* ***Where:*** *Room S105bc.* ***Access:*** *Academy Plus course pass.*
- "Contract Negotiations: How to Protect Your Practice's Best Interests—In Memory of Brenda Laigaie, Esq." (506). Brenda Laigaie was an expert in health law and a frequent speaker and trusted advisor for the American Academy of Ophthalmic Executives. ***When:*** *Monday, Oct. 29, 3:15-4:15 p.m.* ***Where:*** *Room S103d.* ***Access:*** *Academy Plus course pass.*

Buy a ticket for a special event. The following sessions require tickets that must be purchased separately:

- "(Re)Focus on Remarkable Patient Care Experiences" (Spe02). ***When:*** *Friday, Oct. 26, 1:30-4:30 p.m.* ***Where:*** *Room S106a.* ***Access:*** *Ticket required.*
- "The Profitable Practice: Six Proven Turnaround Strategies" (Spe03). ***When:*** *Saturday, Oct. 27, 1:30-4:30 p.m.* ***Where:*** *Room S105d.* ***Access:*** *Ticket required.*

Attend a free roundtable. Learn from your colleagues through discussions focused on top issues facing ophthalmic practices. Attend:

- "Hot Topics Practice Management Roundtables" (Spe11). ***When:*** *Sunday, Oct. 28, 8:00-9:45 a.m.* ***Where:*** *Room S103bc.* ***Access:*** *AAOE members.*
- "Hot Topics Practice Management Roundtables" (Spe26). ***When:*** *Monday, Oct. 29, 12:30-1:45 p.m.* ***Where:*** *Room S103bc.* ***Access:*** *AAOE members.*

Plan your schedule. To explore the full program, use the Mobile Meeting Guide at aao.org/mobile.

SUBSPECIALTY DAY

Subspecialty Day Previews: What's Hot

This month, program directors from the Refractive Surgery Subspecialty Day meeting preview some of this year's highlights. View Subspecialty Day program schedules on the Mobile Meeting Guide at aao.org/mobile.

REFRACTIVE SURGERY 2018: Better Together—Lens- and Cornea-Based Surgery

Program directors: *William B. Trattler, MD, and Marcony R. Santhiago, MD.* ***When:*** *Friday, Oct. 26, 7:15 a.m.-5:30 p.m.*

"Refractive Surgery Subspecialty Day is a comprehensive, 1-day program with an outstanding faculty. The meeting starts with a 'Breakfast With the Experts,' when attendees can discuss interesting cases 1-on-1 with 30 faculty members. The 15 topics include laser vision correction enhancement, pearls

for toric IOLs, femtosecond LASIK, and combining photorefractive keratectomy with corneal cross-linking.

"Following breakfast, the first session will focus on corneal and intraocular refractive procedures, moderated by William B. Trattler, MD, and Kendall E. Donaldson, MD. The keynote lecture will be given by Marguerite B. McDonald, MD, who will reflect on 30 years of laser vision correction and the challenges she faced getting laser vision correction started. The session will continue with a series of lecturers, including Renato Ambrosio Jr., MD, who will discuss 'Advances in Preoperative Assessment for Corneal Refractive Surgery,' and George O. Waring IV, MD, who will discuss 'Refractive Index Reshaping of the Lens.'

"Following a break, International Society of Refractive Surgery (ISRS) President John So-Min Chang, MD, will announce the ISRS Awards, including the José Barraquer Award and the Troutman Prize.

"The second session is titled 'Management and Prevention of Complications in Refractive Surgery,' and will be moderated by Marcony R. Santhiago, MD, and Dr. McDonald. Highlights include lectures by Jack T. Holladay, MD, who will speak on 'Pearls and Pitfalls in Biometry Following Corneal Refractive Surgery or Keratoconus,' as well as Vance Michael Thompson, MD, who will cover how to communicate with patients who are not satisfied with their visual outcomes.

"Lunch, which is included in the meeting's cost of attendance, will follow the second session. An ISRS members' lunch will offer a focused session on optimizing success with presbyopic lenses moderated by Dr. Chang.

"Immediately following lunch, Amar Agarwal, MD, and Jennifer M. Loh, MD, will moderate one of the highlights of the meeting: a video-based masters complications session, which will feature an extensive list of cases, including the management of intraoperative challenges during LASIK, presented by A. John Kanellopoulos, MD, and how to manage phakic IOLs, presented by Alaa M. ElDanasoury, MD.

"The European Society of Cataract and Refractive Surgeons (ESCRS) will then host a mini-symposium on small-lenticule extraction, with the title 'Will Small-Lenticule Extraction Replace LASIK?' Beatrice Cochener, MD, will moderate this session.

"Following the ESCRS session, attendees can enjoy refreshments during a 'Break With the Experts,' when faculty members will discuss 15 topics.

"The final session, '*JRS*: Hot, Hotter, Hottest: Late-Breaking News,' will feature innovative techniques and technologies for refractive surgery. J. Bradley Randleman, MD, and Soosan Jacob, FRCS, will moderate this session.

"While the overall program is extensive, time is built in to foster interaction with faculty and answer questions."

The Refractive Surgery meeting is the annual meeting of the International Society of Refractive Surgery (ISRS).

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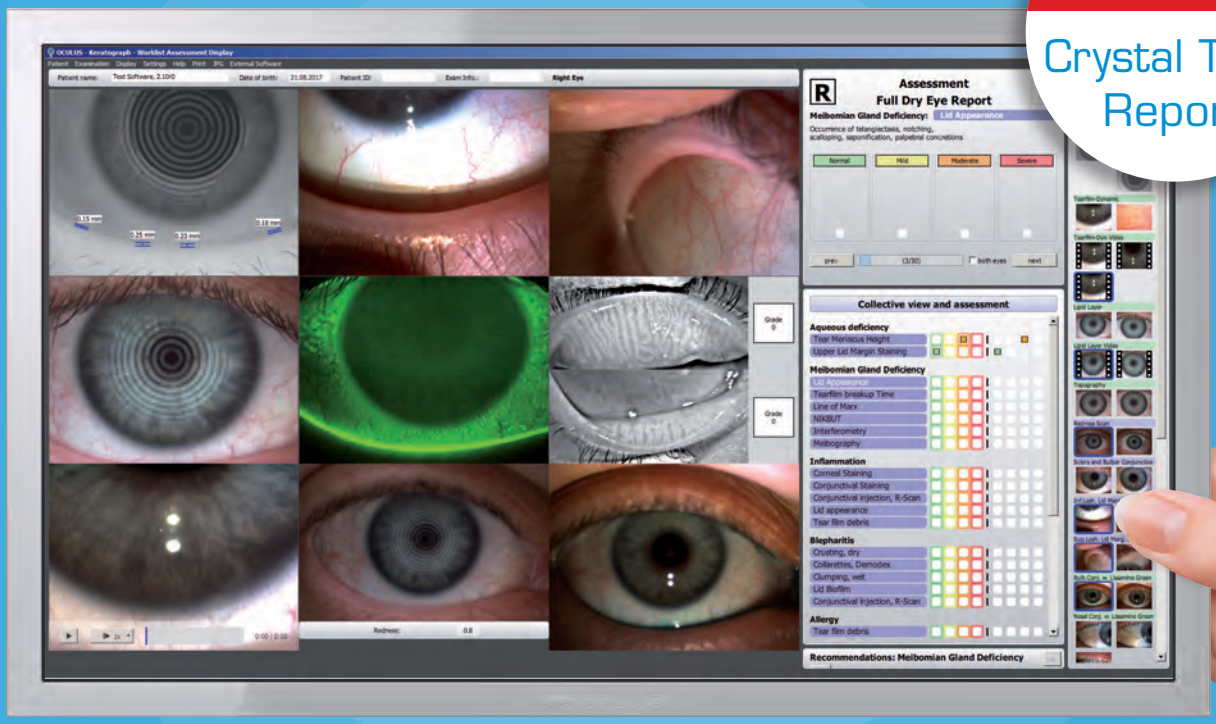

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#1 Branded Prescribed Ophthalmic NSAID[1]

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For as little as $15, eligible patients can access proven efficacy for post-cataract-surgery pain and inflammation.[2,*]

- Inflammation completely cleared in 61% to 65% of patients at day 14[3,†,‡]
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ILEVRO® Suspension is the only prodrug NSAID formulated for once-daily cataract post-op use.[2,4-6]

Dosage and Administration
One drop of ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery. Use of ILEVRO® Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.

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INDICATIONS AND USAGE
ILEVRO® (nepafenac ophthalmic suspension) 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

For additional information about ILEVRO® Suspension, please refer to the Brief Summary of Prescribing Information on the adjacent page.

*Limitations apply. Please see co-pay savings materials for details.

†**Study Design:** Results from 2 randomized, multicenter, controlled, double-masked trials of adult patients undergoing cataract extraction. In Study 1, patients were randomized to receive either ILEVRO® Suspension (n=851), NEVANAC® Suspension (n=845), ILEVRO® Suspension vehicle (n=211), or NEVANAC® Suspension vehicle (n=213). In Study 2, patients were randomized to receive either ILEVRO® Suspension (n=540) or ILEVRO® Suspension vehicle (n=268).[2,3]

‡61% to 65% with ILEVRO® Suspension versus 24% to 32% with vehicle; $P<0.05$.

§84% to 86% with ILEVRO® Suspension versus 38% to 46% with vehicle; $P<0.05$.

References: 1. Data on file. IMS Health. **2.** ILEVRO (nepafenac ophthalmic suspension) 0.3% [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2014. **3.** Data on file. Novartis Pharmaceuticals Corporation; 2011. **4.** BromSite (bromfenac ophthalmic solution) 0.075% [package insert]. Cranbury, NJ: Sun Pharma Global FZE; 2016. **5.** Prolensa (bromfenac ophthalmic solution) 0.07% [prescribing information]. Bridgewater, NJ: Bausch & Lomb; 2016. **6.** NEVANAC® (nepafenac ophthalmic suspension) 0.1% [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2017.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

8/18

T-ILV-1357362

ILEVRO* (nepafenac ophthalmic suspension), 0.3%, topical ophthalmic
Initial U.S. Approval: 2005

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

1 INDICATIONS AND USAGE

ILEVRO* (nepafenac ophthalmic suspension), 0.3% is indicated for the treatment of pain and inflammation associated with cataract surgery.

4 CONTRAINDICATIONS

ILEVRO* (nepafenac ophthalmic suspension), 0.3% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Bleeding Time

With some nonsteroidal anti-inflammatory drugs including ILEVRO* (nepafenac ophthalmic suspension), 0.3%, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.

It is recommended that ILEVRO* (nepafenac ophthalmic suspension), 0.3% be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.2 Delayed Healing

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO* (nepafenac ophthalmic suspension), 0.3%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.3 Corneal Effects

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO* (nepafenac ophthalmic suspension), 0.3% and should be closely monitored for corneal health.

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

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

5.4 Contact Lens Wear

ILEVRO* (nepafenac ophthalmic suspension), 0.3% should not be administered while using contact lenses.

6 ADVERSE REACTIONS

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

6.1 Serious and Otherwise Important Adverse Reactions

The following adverse reactions are discussed in greater detail in other sections of labeling.

- Increased Bleeding Time (*Warnings and Precautions 5.1*)
- Delayed Healing (*Warnings and Precautions 5.2*)
- Corneal Effects (*Warnings and Precautions 5.3*)

6.2 Ocular Adverse Reactions

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

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

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

6.3 Non-Ocular Adverse Reactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects.

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

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO* (nepafenac ophthalmic suspension), 0.3% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.

Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO* (nepafenac ophthalmic suspension), 0.3% during late pregnancy should be avoided.

8.3 Nursing Mothers

Nepafenac is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO* (nepafenac ophthalmic suspension), 0.3% is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of ILEVRO* (nepafenac ophthalmic suspension), 0.3% in pediatric patients below the age of 10 years have not been established.

8.5 Geriatric Use

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

U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767

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MYSTERY IMAGE

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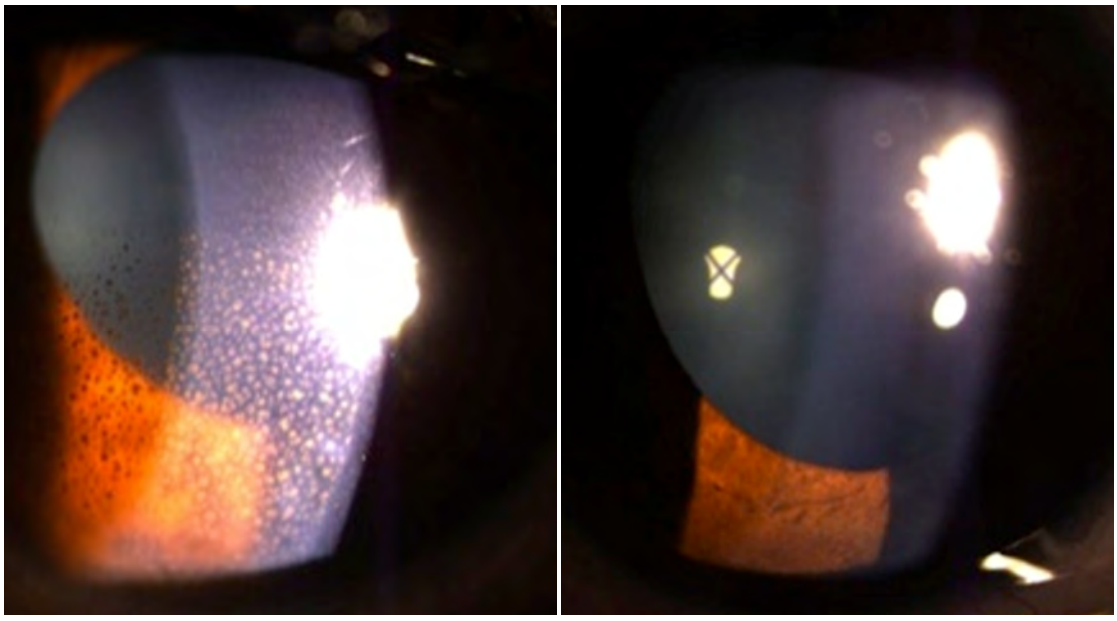


Arun Kapil, Advanced Eye Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

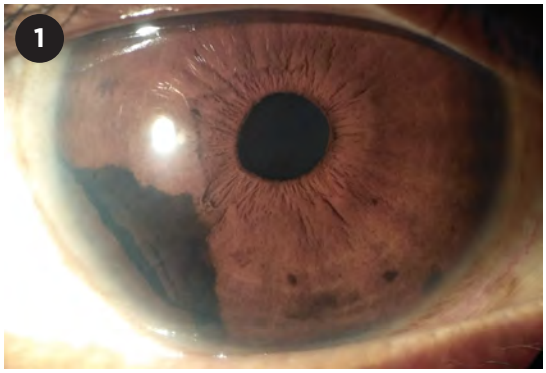
WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments and get the answer to last month's mystery.*

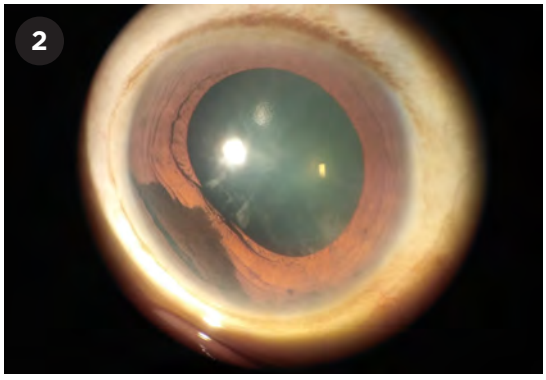
LAST MONTH'S BLINK

Iris Melanoma

A 59-year-old woman came to our clinic for a routine eye examination. On slit-lamp exam, a hyperpigmented iris lesion was noted in her right eye (Fig. 1). The lesion was seen inferotemporally with a feathery margin and iridocorneal involvement with corneal touch. A mild degree of corectopia was also noted. Gonioscopy showed tumor seeding in all quadrants. On dilation (Fig. 2), a localized secondary cataract was noted underneath the lesion. Fine-needle aspiration biopsy and ultrasound biomicroscopy provided confirmation of melanoma.

Iris melanoma is rare, representing 2% of all uveal melanomas, in contrast to iris nevus, which is common. Iris melanoma should be diagnosed quickly and treated promptly. Treatment can be in the form of sector iridectomy/iridocyclectomy, radioactive plaque brachytherapy, or enucleation. Metastasis can be seen in 2%-10% of all iris melanoma cases. It can be asymptomatic at presentation, as in our case, or the patient may notice a sudden increase in size of a preexisting nevus and may have cosmetic concerns, pain, change in vision, or raised intraocular pressure. The melanoma can be circumscribed or diffuse, sometimes involving more than two-thirds of the angle (ring melanoma). The ABCDEF guide for predicting if an iris nevus could become melanoma is: Age <





40 years. Blood in anterior chamber. Clock hour: inferior. Diffuse configuration. Ectropion/corectopia. Feathery margin. Other risk factors: angle involvement, secondary cataract, or glaucoma.

WRITTEN BY **ROOPASHREE HARIPRASAD VOKUDA, MD,** AND **HARIPRASAD VOKUDA, MD,** SHREE HARI NETRALAYA, UDUPI, INDIA. PHOTOS BY **DR. HARIPRASAD VOKUDA.**

LUCENTIS®
RANIBIZUMAB INJECTION

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

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

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

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

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

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

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

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

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

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

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

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

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

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

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

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

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

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

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

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

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

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

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

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

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

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

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

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

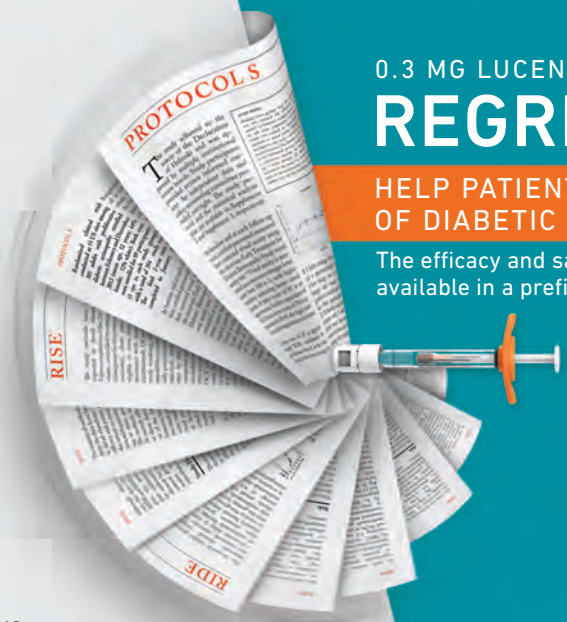
8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in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

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

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

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

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017



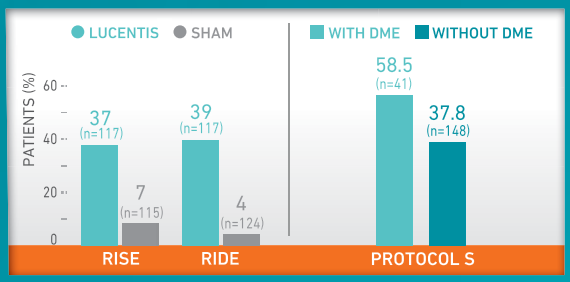
0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED[1]

HELP PATIENTS TURN BACK TO AN EARLIER STAGE OF DIABETIC RETINOPATHY (DR)[1]

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a prefilled syringe.[1]

≥2-STEP IMPROVEMENTS AT 2 YEARS[1]*



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

RISE AND RIDE
- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S
- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).[1]

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
- Diabetic retinopathy (DR)
- Diabetic macular edema (DME)

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)
- In a pooled analysis of Studies DME-1 and DME-2, 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
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, 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

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
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

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

*The following clinical trials were conducted for the **DR & DME** indications: ***RISE & RIDE***—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. ***Protocol S***—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.[2-3]

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).[1]

DME, diabetic macular edema.

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **2.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **3.** Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

Genentech
A Member of the Roche Group

LUCENTIS®
RANIBIZUMAB INJECTION