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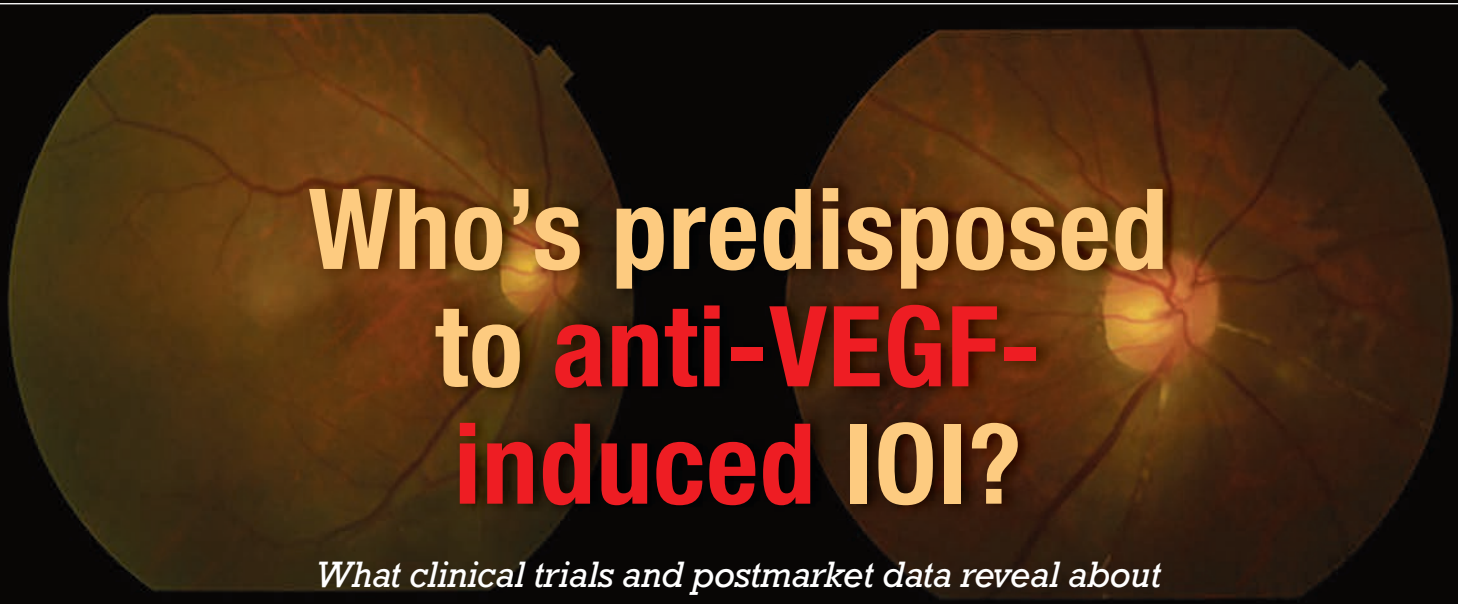


Who's predisposed to anti-VEGF-induced IOI?

What clinical trials and postmarket data reveal about intraocular inflammation risk with brolucizumab. Page 26

Also Inside

Online Video

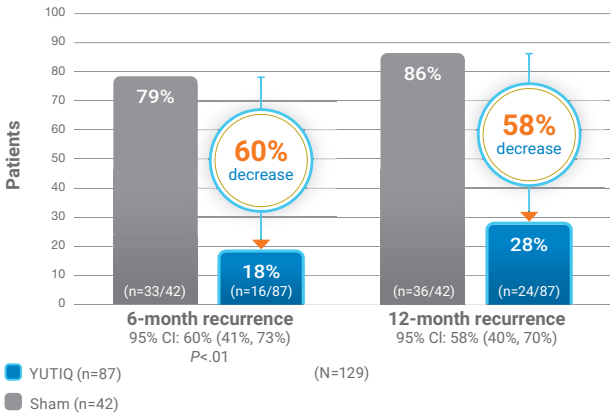
0.18 mg
YUTIQ®
(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover continuous calm in uveitis[1]

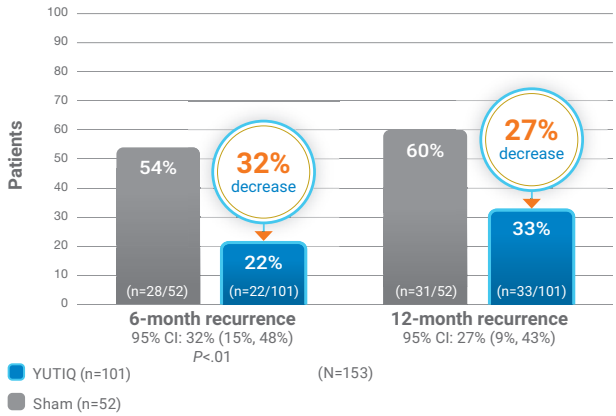
The durability of YUTIQ reduced the recurrence of posterior segment uveitis[1]

For patients with chronic non-infectious uveitis affecting the posterior segment of the eye, YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is designed to deliver a sustained release of fluocinolone for up to 36 months.[1]

Study 1: Patients with uveitis recurrence at 6 and 12 months[1]



Study 2: Patients with uveitis recurrence at 6 and 12 months[1]



CI=confidence interval.

Analyses of the rate of uveitis reduction at 36 months are ongoing

Study overview: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, phase 3 studies in adult patients (N=282) with non-infectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis, or the use of confounding medications.[1,2]

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

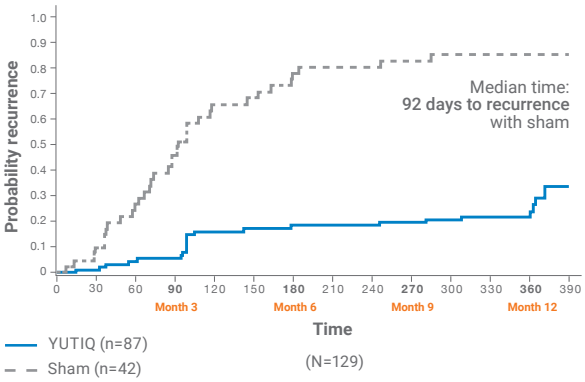
CONTRAINDICATIONS

Ocular or Periocular Infections: YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Hypersensitivity: YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

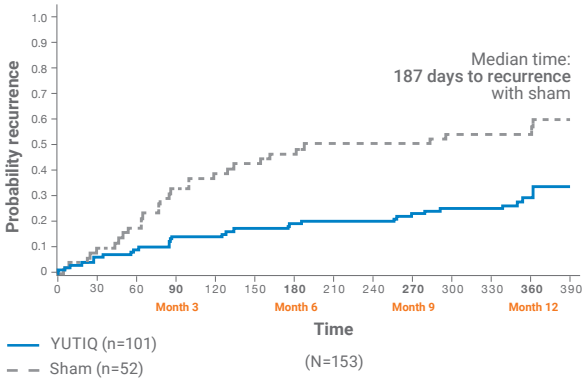
YUTIQ increased the time to next recurrence of posterior uveitis[1]

Study 1: Time to first recurrence of uveitis in the study eye within 12 months[1,2]



(N=129)

Study 2: Time to first recurrence of uveitis in the study within 12 months[1,2]



(N=153)

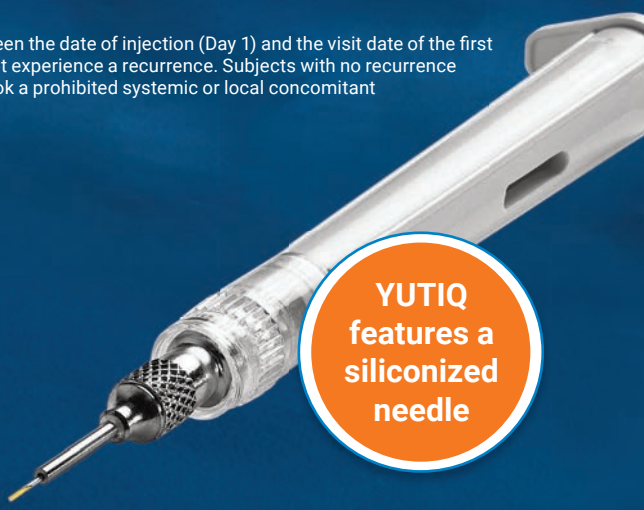
Median time to recurrence with YUTIQ was too low to evaluate.[2]

Analysis of median time to first recurrence[2]

Time to first recurrence of uveitis within 12 months was calculated as the number of days between the date of injection (Day 1) and the visit date of the first reported recurrence of uveitis in the study eye or the Month 12 visit date for subjects who did not experience a recurrence. Subjects with no recurrence prior to Month 12 who did not have recurrence assessed at Month 12 (for any reason) or who took a prohibited systemic or local concomitant medication prior to Month 12 were counted as having a recurrence of uveitis.

Offer your patients the calm they need

YUTIQ.com



IMPORTANT SAFETY INFORMATION *(cont'd)*

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

Please see next page for Brief Summary of full Prescribing Information.

References: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full US Prescribing Information. May 2021. **2.** Data on file. EyePoint Pharmaceuticals, Inc.

EyePoint PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472

05/2021
US-YUT-2100082

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

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

1. INDICATIONS AND USAGE. YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. Clinical Studies Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

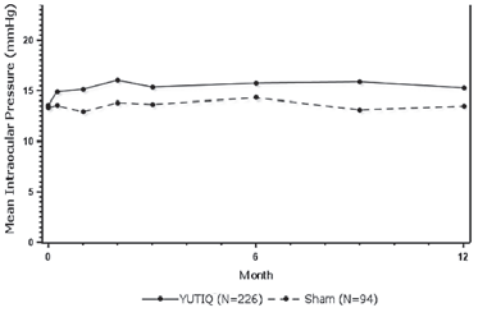
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Manufactured by:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
Patented.

RETINA
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Jobson Medical Information

EDITORIAL

By Charles C. Wykoff, MD, PhD

Making the pivot

Forced to transition from in-person to virtual, we've been here before, many times since February 2020. But this time it wasn't due to COVID-19. As the Caldor Fire in California exploded toward Lake Tahoe, air quality plummeted beyond the Very Unhealthy zone into Hazardous, and evacuations began. Five days before the inaugural Clinical Trials at the Summit conference, aimed at bringing together physicians and industry leaders focused on the clinical trial ecosystem, the meeting went virtual.

We've become fairly good at pivoting, likely due to so many opportunities to practice. As parents we pivoted to the virtual classroom with our kids and continue to adapt within our nation's fragmented education system. As international travelers, we learned about NAVICA, the digital platform for rapid COVID-19 testing; attestation forms; polymerase chain reaction test turnaround times (with exorbitant fees); and each destination's unique testing and quarantine requirements. As physicians, we learned to minimize risk of exposure while cautiously starting to reengage pre-pandemic routines.

Within the last month two friends, a retina specialist and a general practitioner, contracted COVID-19 despite being double vaccinated. One was quite ill but didn't need hospitalization. In response, I pivoted and got my Pfizer booster at the end of August, earlier than I had planned.

Despite a full Food and Drug Administration approval, with others anticipated to follow, and an overwhelmingly positive benefit-to-risk ratio, many are still resistant to vaccination. The proportion of anti-vaxxers in my clinic is not trivial, even among high-risk populations. The inpatient COVID-19 census at my hospital, Houston Methodist, is near its peak. The large majority of these patients, many dying, are unvaccinated.

I'm embarrassed to admit that only about 70 percent of my clinic staff are vaccinated. As medical systems and prominent companies embrace vaccine mandates, I'm encouraging my employees to get vaccinated; if not, we will likely pivot to a mandate.

On the medical side, what will it take for you to pivot to a new therapy for your exudative AMD patients? Presumably the risk of intraocular inflammation with brolucizumab, as detailed by Drs. Huy Nguyen and Michael Singer on page 26, is too high to recommend it for most patients. When the Port Delivery System (PDS) with ranibizumab is commercially available, what safety profile will be tolerable for the benefit of fewer intravitreal injections longitudinally? With faricimab, will you pivot first with your incomplete responders?

On page 38, Dr. Sunir Garg details key ergonomic considerations to maximize your health, and I think he would recommend not pivoting too much!

Will the upcoming annual Retina Society, American Society of Retina Specialists and American Academy of Ophthalmology conferences really happen in person? I hope so. But, we will be ready to pivot if we need to.

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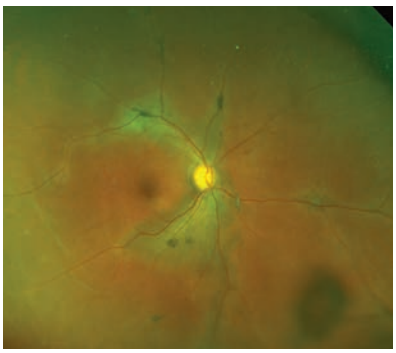
FEATURES

COVER STORY

DEPARTMENTS



New research challenges previous findings on genetic risk factor for AMD

Recently published findings of the role of a key genetic protein in the pathogenesis of age-related macular degeneration challenges existing thinking about how the protein contributes to disease progression.

Researchers at the University of Utah reported that mRNA encoding the serine protease *HTRA1* in people with a genetic predisposition to AMD is the strongest genetic risk factor for disease progression.[1] They've concluded that enhancing expression of the underlying HtrA1 protein—it stands for high-temperature requirement A1—would be a desirable target to treat AMD.

The researchers noted their observations contradict previously published reports that showed either no difference or elevated expression of HtrA1 in retinal tissue from donors with 10q26 risk.[2,3] Based on that research, Genentech applied for a patent on anti-HtrA1 antibodies and is conducting Phase II trials of the candidate FHTR2163, an intravitreal treatment that targets this novel pathway in geographic atrophy secondary to dry AMD.

"While the specific role and impact of HtrA1 in geographic atrophy has not yet been fully established in a randomized clinical trial, multiple preclinical studies have shown that over-expression of *HTRA1* in the retina is associated with atrophy of the retinal pigment epithelium and photoreceptors," Genentech says in a statement.

Brandi Williams, PhD

"Thus, it remains reasonable to hypothesize that geographic atrophy progression may be associated with elevated HtrA1 levels in the retina," the company says. It cites a Phase I trial that showed anti-HtrA1 is safe in humans, and notes that the ongoing Phase II GAllego and GAllegOLE trials "will provide further data on safety and efficacy of anti-HtrA1, and should further our understanding of HtrA1's role in geographic atrophy."

Role of HtrA1 protein

Studying what they described as a "extensive repository of donated human ocular tissues," the Utah researchers reported that the HtrA1 protein increases with age in the retinal pigment epithelium-Bruch's membrane interface, helping to maintain normal function in the region, in donor eyes with the 10q26 (Chr10) locus, which has been identified as the strongest genetic risk factor for AMD. The 10q26 locus contains the *ARMS2* and the *HTRA1* genes.

The repository consists of more than 8,000 pairs of donated human eyes at the University of Utah's Sharon Eccles Steele Center for Translational Medicine (SCTM). "One of the huge strengths of the study was that we were using human donor tissue, not a cell culture model nor differentiated RPE cells," lead author Brandi Williams, PhD, tells *Retina Specialist*. "Hundreds of samples were used. We found a huge range of expression, but the effect is small, so having as many as samples as we had really solidifies the findings."

She notes that previous studies used few samples and didn't observe any differences in retinal tissues. "We really felt we observed a tissue-specific effect," Dr. Williams says. The researchers developed a specific assay to confirm their findings.

Focus of future research

The Utah study examined donor eyes that didn't have AMD. Chr10 is

(Continued on page 11)

IN BRIEF

Samsung Bioepis' Byooviz, also known as **SB11**, has become the first ranibizumab biosimilar approved by the European Union, The Center for Biosimilars reports. Byooviz references **Lucentis**, which is distributed by **Novartis** in Europe.

Ocular Therapeutix reports dosing the first patient in the U.S. Phase I clinical trial of the intravitreal axitinib implant **OTX-TKI** for wet age-related macular degeneration. The trial is evaluating a single OTX-TKI implant containing a 600-µg dose of axitinib, compared with a 2-mg dose of **aflibercept** q8 weeks in previously treated patients. It will enroll 20 patients; 15 in the OTX-TKI arm and five in the aflibercept arm.

Results of an ongoing Phase II proof-of-concept trial evaluating an investigational 8-mg dose of **aflibercept** met its primary safety endpoint, **Regeneron Pharmaceuticals** reports. The study involving 106 patients identified no new safety signals compared to the currently-approved 2-mg dose of Eylea in 106 wet AMD patients.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

36 FAMILY RECIPES

Inspired by a real patient with MEfRVO.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

CLINICALLY SIGNIFICANT VISION GAINS IN MEfRVO ACROSS 3 ROBUST CLINICAL TRIALS

Proportion of patients who gained ≥15 ETDRS letters (primary endpoint) and mean change in BCVA (ETDRS letters) (secondary endpoint) at Month 6 from baseline vs control[1-4,*]

VIBRANT (MEfBRVO)		COPERNICUS (MEfCRVO)		GALILEO (MEfCRVO)	
Gained ≥15 ETDRS letters	Mean change in ETDRS letters	Gained ≥15 ETDRS letters	Mean change in ETDRS letters	Gained ≥15 ETDRS letters	Mean change in ETDRS letters
EYLEA (n=91)	**EYLEA (n=91)**	**EYLEA (n=114)**	**EYLEA (n=114)**	**EYLEA (n=103)**	**EYLEA (n=103)**
53% vs 27% in the control group (n=90)	**+17.0** vs +6.9 in the control group (n=90)	**56%** vs 12% in the sham control group (n=73)	**+17.3** vs -4.0 in the sham control group (n=73)	**60%** vs 22% in the sham control group (n=68)	**+18.0** vs +3.3 in the sham control group (n=68)

P<0.01 vs control and sham control.

VIBRANT study design: Randomized, multicenter, double-masked, controlled study in which patients with MEfBRVO (N=181; age range: 42-94 years, with a mean of 65 years) were randomized to receive: 1) EYLEA 2 mg Q4 or 2) laser photocoagulation administered at baseline and subsequently as needed (control group). The primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.[1]

COPERNICUS and GALILEO study designs: Randomized, multicenter, double-masked, sham-controlled studies in patients with MEfCRVO (N=358; age range: 22-89 years, with a mean of 64 years). Patients were assigned in a 3:2 ratio to either: 1) EYLEA 2 mg Q4 for the first 6 months or 2) sham injections (control) Q4 for a total of 6 injections. In both studies, the primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.[1]

*Last observation carried forward; full analysis set.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH MEfRVO AT HCP.EYLEA.US

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology*. 2015;122(3):538-544. doi:10.1016/j.ophtha.2014.08.031 **3.** Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology*. 2012;119(5):1024-1032. doi:10.1016/j.ophtha.2012.01.042 **4.** Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol*. 2013;97(3):278-284. doi:10.1136/bjophthalmol-2012-301504

03/2021
EYL.21.02.0050

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

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

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

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

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

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

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

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

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EYL.20.09.0052

Genetic risk factor for AMD

(Continued from page 7)

a risk factor for both forms of AMD, Dr. Williams says, and the under-expression of *HTRA1* can drive both forms of the disease. Dr. Williams adds that HtrA1 may have a role in maintaining healthy vasculature and that its under-expression may contribute to other vascular diseases.

The Utah research team is focusing on further investigating the functional effects HtrA1 has in the RPE-Bruch's membrane interface and is pursuing proof-of-concept studies for gene therapy approaches for enhancing *HRTA1* expression.

Dr. Williams and other co-authors are inventors on patents and patent applications owned by the University of Utah.

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Retina Specialist welcomes five to editorial board

Retina Specialist magazine has expanded its editorial board with the addition of five new board members. They are:

• ***Caroline Baumal, MD,*** professor of ophthalmology at New England Eye Center, Tufts Medical Center in Boston. She specializes in medical and surgical disorders of the retina and vitreous, with research interests focusing on novel retinal imaging and drug development.

• ***Justis P. Ehlers, MD,*** the Norman C. and Donna L. Harbert Endowed Chair of Ophthalmic Research and director of the Tony and Leona Campane Center for Excellence in Image-Guided Surgery and Advanced Imaging Research at the Cole Eye Institute of the Cleveland Clinic. Dr. Ehlers' clinical expertise is in the treatment and management of vitreoretinal diseases and advanced ophthalmic imaging.

• ***Avni Finn, MD, MBA,*** a vitreoretinal surgeon with Northern California Retina Vitreous Associates in the San Francisco Bay area. Among Dr. Finn's research interests are new techniques for macular hole surgery, intraoperative optical coherence tomography imaging, and biomarkers of atrophy and scar in macular degeneration.

• ***Mrinali Gupta, MD,*** a vitreoretinal surgeon at Retina Associates of Orange County, with offices in Newport Beach, Laguna Hills and Santa Ana, Calif. Previously, Dr. Gupta served for five years as vitreoretinal surgeon and assistant professor of ophthalmology at Weill Cornell Medical College in New York. Dr. Gupta currently serves as vice president of education on the executive committee of the Vit-Buckle Society.

(Continued on page 17)

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Not just pigments of your imagination

A case of idiopathic intrigue requiring investigation of an inflammatory cause.

By Jacob Light, MD, and Jason Hsu, MD

Jacob Light, MD,

Jason Hsu, MD

A 68-year-old man with history of hypertension, type 2 diabetes (without prior retinopathy) and psoriasis presented to the emergency department for blunt trauma to the right eye following an assault. His ocular history was negative aside from a history of uncomplicated cataract extraction with intraocular lens placement in both eyes eight years earlier.

Ophthalmic consultation revealed findings consistent with traumatic mydriasis and iritis in the affected right eye. Topical prednisolone and cycloplegics were prescribed. However, a dilated exam revealed abnormalities of both fundi, so the patient was referred to the ophthalmology clinic for further evaluation.

Clinical evaluation

On evaluation in the clinic one week later, visual acuity with correction was 20/40 in both eyes. Intraocular pressures were 17 mmHg OD and 22 mmHg OS. The right pupil was dilated and sluggish, consistent with prior diagnosis of traumatic mydriasis. There was no relative afferent pupillary defect by reverse testing.

An anterior segment examination of both eyes revealed well-centered posterior chamber intraocular lenses with trace pigment in the formed anterior vitreous, but no inflammatory cells or vitritis.

The fundus examination showed bilateral hypopigmentation emanating from the discs and extending out along the major superior and inferior arcades, with additional hypopigmentation noted along the nasal venules (*Figure 1*). Clumps of hyperpigmentation were also seen within the regions of hypopigmentation and were concentrated adjacent to the major retinal veins. A full scleral-depression exam showed no retinal tears or detachments or any vitreous snowballs or snow-banking in either eye.

Role of multimodal imaging

Multimodal imaging helped to further characterize the pigmentary changes. Widefield fundus autofluorescence imaging was notable for marked hypoautofluorescence corresponding to the regions of hypopigmentation described on the fundus exam, with strongly hyperautofluorescent borders (*Figure 2*).

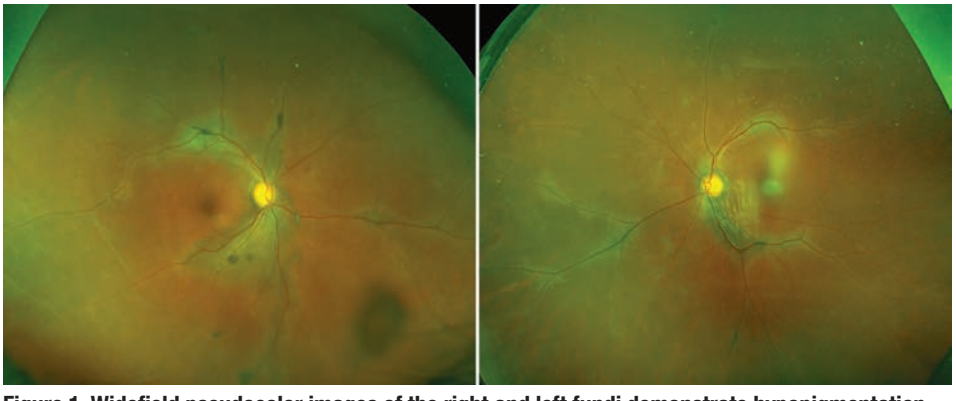

Figure 1. Widefield pseudocolor images of the right and left fundi demonstrate hypopigmentation of the retinal pigment epithelium extending from the disc along the major arcades, with additional foci along the nasal vasculature. Clumps of hyperpigmentation are seen in both fundi, predominantly along the retinal veins.

Bios

Dr. Light a clinical vitreoretinal surgery fellow at Wills Eye Hospital, Philadelphia.

Dr. Hsu is with Mid Atlantic Retina/ Retina Service, Wills Eye Hospital.

DISCLOSURES: Drs. Light and Hsu have no relevant financial relationships to disclose.

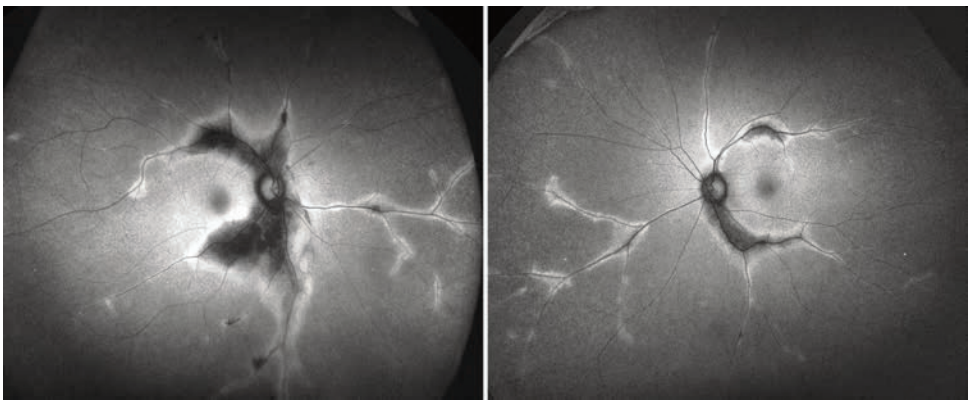

Figure 2. Widefield fundus autofluorescent imaging of the right and left fundi demonstrate marked hypoautofluorescence that corresponds to the hypopigmentation seen on color fundus exam. The lesions show well-defined hyperautofluorescent borders.

Optical coherence tomography scans in the central macula showed preservation of normal inner and outer retinal lamination patterns (*Figures 3A,B*). But severe atrophy of the retinal pigment epithelium and choriocapillaris, with associated photoreceptor layer loss, were evident in the areas of peripheral macular pigmentary change (*Figures 3C,D*). No subretinal or intraretinal fluid was apparent.

We also obtained widefield fluorescein angiography. Early frames revealed normal arterial and venous filling times with scattered microaneurysms and areas of peripheral capillary dropout, consistent with subclinical nonproliferative diabetic retinopathy. Large areas of hyperfluorescence, consistent with window defects, were seen along the proximal arcades (*Figures 4A,B, page 14*). Late frames demonstrated patchy interstitial leakage in the macula and periphery with persistent window defects and/or staining in the regions of fundus pigmentary changes (*Figures 4C,D, page 14*). Hyperpigmented clumps corresponded to signal blockage on the angiogram. No disc or vascular leakage was apparent in either eye.

Due to the borderline cup-to-disc ratios and asymmetric tonometry mentioned previously, we obtained a 24-2 Humphrey visual field. While no glaucomatous

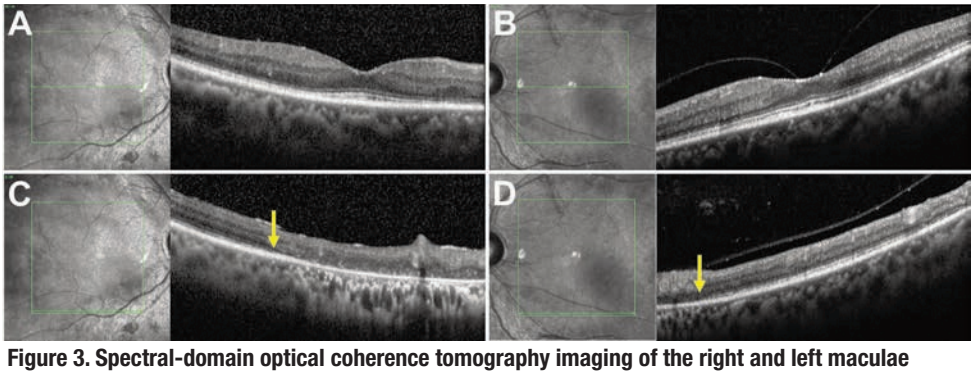

Figure 3. Spectral-domain optical coherence tomography imaging of the right and left maculae with corresponding *en face* infrared reflectance images show preservation of outer retinal lamination patterns in the central macula and fovea in the right (A) and left (B) eyes, respectively. Line scans through the right (C) and left (D) inferior maculae show outer-retinal atrophy nasally (arrows indicate border of intact and missing external limiting membrane), corresponding to the hypopigmentation seen on the fundus exam.

Optical coherence tomography scans in the central macula showed preservation of normal inner and outer retinal lamination patterns.

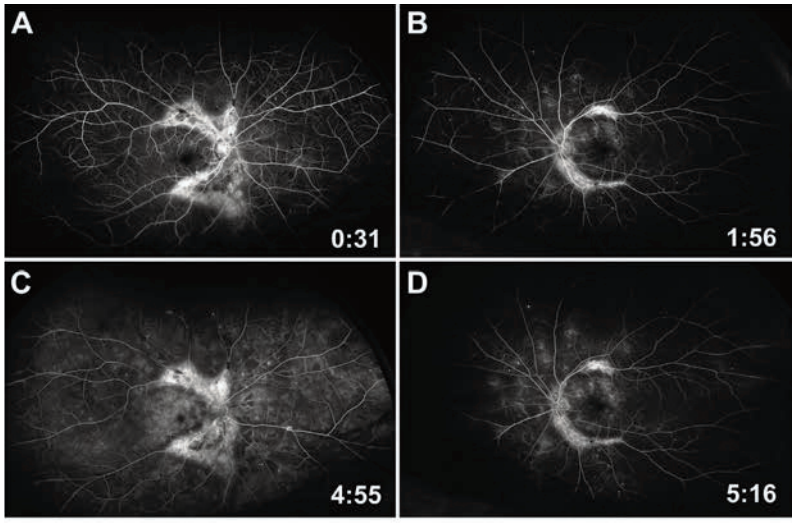

Figure 4. Early-to-mid frames of widefield fluorescein angiography of the right (A) and left (B) eye show clear window defects in the areas of fundal hypopigmentation, with intact arterial and venous filling. Late frames (C and D) reveal persistent window defects and staining. Background nonproliferative diabetic retinopathy and subclinical macular edema are also seen in both eyes.

defects were seen, the results demonstrated profound sensitivity loss in a temporal horseshoe-like pattern, corresponding topographically to the areas of outer retinal atrophy (*Figure 5, page 16*).

Broad differential, classic look

Given the large areas of outer retinal, RPE and choriocapillaris atrophy along with significant visual field loss, we carefully considered a differential diagnosis that included infectious, inflammatory, dystrophic and degenerative etiologies.

The atrophic changes concentrated in the vascular distribution suggested the possibility of a "burned out" infectious or inflammatory vasculitis, which may be associated with herpes viruses, syphilis, tuberculosis, sarcoidosis or Behçet's disease. We also considered serpiginous choroiditis and acute zonal occult outer retinopathy (AZOOR). In the category of dystrophies or degenerations, a retinitis pigmentosa variant, cone-rod dystrophies and atypical geographic atrophy were candidate diagnoses.

Ultimately, after a literature review and consultation with uveitis specialists, we concluded the findings were classic for pigmented paravenous retinochoroidal atrophy (PPRCA).

Pathology of PPRCA

PPRCA was first described in 1937 by T. Hewiston Brown, MC, ChB, in a 47-year-old man with alopecia areata.[1] Since its initial description, this clinical entity has been described by several different names, including retinochoroiditis radiata, pseudoretinitis pigmentosa, chorioretinitis striata, and congenital pigmentation/melanosis of the retina.[2]

Clinical features are fairly stereotypical and, as seen in our patient, include pigment clumping along retinal venules with associated retinochoroidal atrophy, often involving the peripapillary region, with macular sparing. The lesions are considered to be nonprogressive or only slowly progressive.[3]

Interestingly, the majority of case reports of PPRCA have been in male patients,[4] though the reason for a sex-specific predilection has not been elucidated.

The definitive location of the instigating pathology has not been established, though it has been hypothesized that the disease process has its origin in the RPE.[5] Hypoperfusion and loss of the choriocapillaris layer have been described within areas of pigmentary atrophy in the form of indocyanine green angiography hypocyanescence and OCT angiography flow voids. However, it's unclear whether this phenomenon triggers the outer retinal degeneration or is secondary to it.[6]

What's more, while both FA and ICG-A demonstrate clear RPE and choriocapillaris atrophy, ICG-A has been shown to better detect regions of disease involvement that aren't yet apparent on FA imaging.[7]

Etiology of PPRCA

As its name implies, PPRCA is a descriptive term that characterizes the

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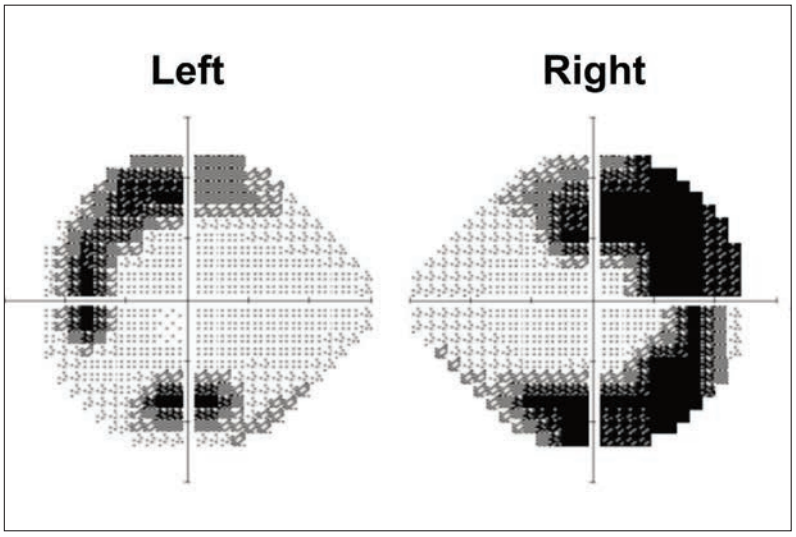

Figure 5. Humphrey visual fields of both eyes with 24-2 protocol. Arcuate temporal field defects crossing both the horizontal and vertical midlines demonstrate greater severity in the right eye than the left.

relevant clinical exam and imaging findings but doesn't give insight into its etiologic underpinnings. Early case reports proposed associations with infectious processes, including tuberculosis,[1] congenital syphilis[8] and measles.[5,9] Others suggested a primary dysgenesis or degenerative process.[10-12]

An interesting published longitudinal case described a 17-year-old girl who developed bilateral sequential acute vision loss with marked retinal edema of the posterior pole.[4] Over the course of the next 20 years, she developed retinal pigmentary changes typical of PPRCA, suggesting that a remote inflammatory insult may indeed be an inciting factor, resulting in this unique clinical phenotype.

However, a comprehensive review proposed that while the findings in PPRCA may be the common end result of any number of infectious or inflammatory insults, the term should be reserved for primary, idiopathic cases, while those cases secondary to other pathology should be designated pseudo-PPRCA.[2]

Investigations in the past few decades have also raised the possibility of an underlying genetic mechanism for PPRCA. Gareth McKay, PhD, and colleagues reported a series of autosomal dominantly inherited cases of PPRCA phenotype in a family with a confirmed mutation in the *CRB1* gene, albeit with variable expression among family members and higher severity in the males.[13]

Other reports have described additional clusters of familial cases, with speculated inheritance ranging from autosomal-dominant or recessive, to X- and even Y-linked patterns.[2] Nevertheless, discordant expression of PPRCA between monozygotic twins has been reported, confirming the complex nature of this clinical phenotype.[14]

Follow-up

Our patient was re-examined at increasing intervals over the next year and found to have complete stability of the pigmentary changes and no decrease in visual acuity.

Cognizant of our inability to distinguish primary, idiopathic PPRCA from pseudo-PPRCA based on clinical phenotype alone, we ordered a focused work-up including tuberculosis and syphilis serologies, as well as chest radiography to rule-out sarcoid-associated hilar lymphadenopathy. Testing revealed no underlying systemic conditions. Following prompt resolution of his initial traumatic iritis, the patient demonstrated no evidence of ocular inflammation at any point during follow-up.

Bottom line

PPRCA is a rare disease, often detected incidentally on routine or unrelated fundus examination. At worst, it's slowly progressive, rarely involving the macula and central vision. At best, it's stationary and asymptomatic for the patient. Multimodal imaging is very useful for confirming its characteristic appearance.

Given the lack of clear etiologic underpinnings and the distinct likelihood that

multiple factors, including those of an infectious or inflammatory nature, may result in a PPRCA-like phenotype, a clinician confronted with such a presentation should obtain a thorough medical history, maintain high clinical suspicion and a broad differential diagnosis, and make efforts to rule out potentially undiagnosed and treatable ocular and systemic conditions. RS

The authors acknowledge Bryn Burkholder, MD, uveitis specialist, and Ravi Pandit, MD, retina specialist, of the Wilmer Eye Institute, Johns Hopkins University, Baltimore, for their expert consultation in this case.

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New board members

(Continued from page 11)

• ***Amir H. Kashani, MD, PhD,*** associate professor of ophthalmology at Wilmer Eye Institute, Johns Hopkins University in Baltimore. His research interests include retinal imaging, and he's the principal investigator of a novel stem cell treatment for geographic atrophy. He was formerly an associate professor and clinical scholar at the University of Southern California.

Breaking down wrong-site injections

Wrong-site intravitreal injections are extremely rare events. The Ophthalmic Mutual Insurance Company reported that it analyzed 51 malpractice claims for intravitreal injections—not specifying the nature of the claims—for the period from 1987 to 2016, while in 2017 alone 7 million such injections were performed.[1] In a recent study published in *JAMA Ophthalmology*, researchers from Kaiser Permanente North California in Oakland reported on four such cases out of more than 147,000 intravitreal injections over two years in their health system.[2]

Nonetheless, they analyzed the errors and identified key lapses in protocol in all the cases. Those lapses included making mistakes in reviewing the electronic medical record, lack of surgeon and staff focus, and inconsistent use of surgical checklists and timeouts.

Lead author Robin A. Vora, MD, of KPNC, explains to *Retina Specialist* the relevance of the findings despite the rare incidence of wrong-site IVI.

"As our population continues to age, the practice of a retina specialist has become increasingly busy," he says. "We serve the growing number of patients who require care for macular degeneration, diabetic retinopathy and other chronic conditions. This comes with an increase in the number of therapeutic choices, along with insurance cost and supply constraints,

Robin A. Vora, MD

and the fact that a single patient may require care in one or both eyes, often at different intervals and with different agents.

"Taken together," Dr. Vora adds, "it becomes clear that precautions must ensure that a physician completes the procedure safely and effectively. This is no different than what all surgeons are required to do in the operating theatre: to ensure the correct procedure to the correct eye. Checklists and 'time-outs' are an essential part of such precautions."

None of the study patients suffered long-term consequences from the erroneous injections. "However," says Dr. Vora, "given that the complication rate for this procedure is non-zero, no future harm is not guaranteed. It's our sincere hope that by sharing our experience, we can inform our colleagues worldwide to adopt safety protocols to make the performance of this common procedure as safe as possible for patients."

Dr. Vora and co-authors have no relationships to disclose. RS

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Department Editor *By Akshay S. Thomas, MD, MS*

Using anti-VEGF agents in uveitis

A review of the available evidence and anecdotal reports supporting their use.

By K. Matt McKay, MD, and Thellea K. Leveque, MD, MPH

K. Matt McKay, MD

Thellea K. Leveque, MD, MPH

Bios

Dr. McKay is a former uveitis fellow and current vitreoretinal surgery fellow at the University of Washington in Seattle.

Dr. Leveque is a clinical professor with a focus on uveitis and comprehensive ophthalmology at the University of Washington, Seattle.

Dr. Thomas is a partner in vitreoretinal surgery and uveitis at Tennessee Retina, with offices in central Tennessee and southern Kentucky.

DISCLOSURES: Drs. Leveque and Thomas have no relevant financial relationships to disclose.

Anti-VEGF intravitreal therapy has revolutionized treatment of exudative macular degeneration, diabetic macular edema, proliferative diabetic retinopathy and retinal vascular occlusion. Its efficacy in treating cystoid macular edema, choroidal neovascularization and retinal neovascularization associated with these diseases is backed by large controlled clinical trials.

Ocular inflammation may be associated with a number of anatomic indications for anti-VEGF agents, including CME, CNV and RNV. This can be due to either active inflammatory disease or secondary structural complications that result from retinal ischemia, chorioretinal scarring or other predisposing factors.[1]

Paucity of evidence in uveitis

While the efficacy of anti-VEGF therapy for exudative macular degeneration, diabetic retinal disease and retinal vascular occlusion has been well established, treatment is more difficult to study systematically in uveitis-related ocular inflammation because of the diversity of uveitic diseases and their varied pathophysiologic mechanisms.

Uveitis specialists rely on case reports, case series and clinical judgment to determine how and when to use anti-VEGF therapy for uveitis, much of which is off-label. This article will discuss the available evidence, such as it is, as well as clinical examples of the use of intravitreal anti-VEGF therapy in uveitis.

Inflammatory control is imperative

Uncontrolled inflammation in uveitis is usually the direct cause of uveitic CME and, occasionally, the direct cause of CNV or RNV. Even in the absence of ischemia, inflamed eyes can develop CNV or RNV, which may be successfully treated with inflammatory control alone.[2-4] Additionally, inflammatory control in occlusive retinal vasculitis may prevent future ischemic RNV, and control of uveitis associated with chorioretinitis may prevent future scar-associated CNV.

After infectious causes have been ruled out or treated, uveitis quiescence must be achieved with local or systemic corticosteroids and may require additional immunosuppressive agents.

Quiet disease may vary in appearance depending on the uveitic type. Slit lamp or indirect biomicroscopy may show improvement in cell and haze or in the morphology and number of chorioretinal lesions. Other signs of disease quiescence may include imaging findings such as improvement in choroidal or retinal thickness by optical coherence tomography; normalization of abnormal fundus autofluorescence; or reduction in vascular leakage or ischemia by indocyanine green angiography or fluorescein angiography may be (*Figure 1*).

Retinal neovascularization

RNV is an infrequent but clinically important complication of uveitis. RNV is significantly more common in uveitis with occlusive vasculitis, such as infectious necrotizing retinitis, systemic lupus erythematosus, Beçhet's disease, idiopathic retinal vasculitis with neuroretinitis (known as IRVAN), tuberculosis-associated retinal vasculitis or Eales disease.[5] Other risk factors include cigarette smoking and young age (≤35 years).[6] In these cases, RNV is often a sign of active inflammation.

Only a few case reports and case series have reviewed the use of anti-VEGF agents for uveitis-associated RNV.[1,7-9] Complete or partial regression of neovascularization was reported in most of these cases. Bevacizumab (Avastin, Genentech/Roche) has been shown to be effective in treating a

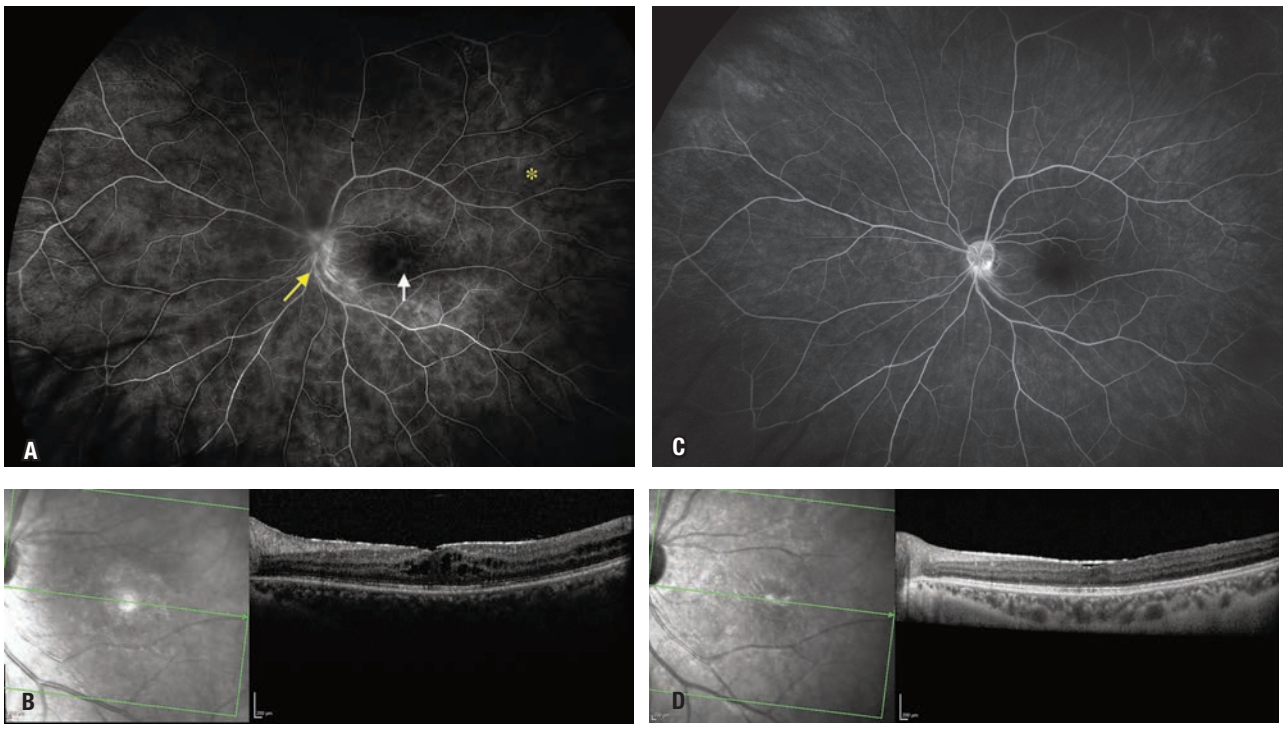

Figure 1. A) Late-phase fluorescein angiography of a 25-year-old patient with active chronic intermediate uveitis showing diffuse small vessel non-occlusive retinal vasculitis (asterisk) and disc leakage (yellow arrow) with associated cystoid macular edema (white arrow). B) Optical coherence tomography image of the patient's CME. C) Late-phase FA of the same patient after uveitis control was achieved via treatment with intravitreal corticosteroid shows resolution of the CME and small-vessel vasculitis, but mild residual disc leakage. D) OCT of the patient's retina after CME resolution. An epiretinal membrane and retinal atrophy are structural consequences of previous chronic disease activity.

recalcitrant uveitic RNV after scatter laser photocoagulation (SLP).[11]

However, clinicians should exercise caution in highly ischemic eyes. This is because anti-VEGF treatments may, in rare cases, close off thread-like vessels providing vital perfusion, paradoxically worsening retinal ischemia. Further study is needed to determine whether SLP, isolated anti-VEGF or combined techniques work best in uveitic RNV (*Figure 2, page 20*).

Choroidal neovascularization

In posterior uveitis and panuveitis, CNV has an incidence and prevalence in the 2 percent range,[12] but it's a hallmark of punctate inner choroiditis (PIC) and multifocal choroiditis (MFC), occurring in up to half of cases.[13] Identifying and treating uveitic CNV can be challenging for two reasons:

- because neovascular membranes and inflammatory lesions at the level of the retinal pigment epithelium-Bruch's membrane (RPE-BM) complex can have similar characteristics on imaging; and
- because angiogenesis may occur in the setting of direct uveitic involvement of the RPE-BM and/or as a result of previous RPE-BM degenerative disruption.[1]

Advanced multimodal imaging analysis and OCT-angiography are useful for evaluating uveitic CNV (*Figure 3, page 22*).[14-16]

Angiogenesis in CNV is a complex process in which inflammatory mediators play

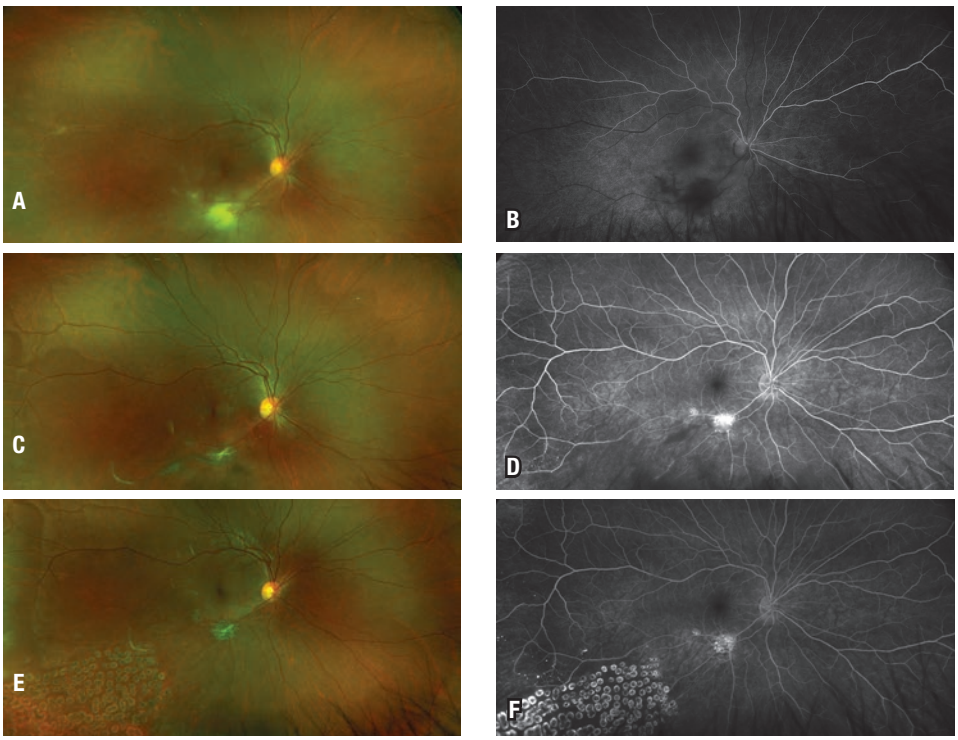

Figure 2. A) Pseudocolor fundus photo of a 32-year-old patient with primary acquired toxoplasmosis retinochoroiditis with an associated occlusive arteriolar vasculitis resulting in an inferior branch retinal artery occlusion. B) Early phase fluorescein angiography demonstrates a large area of inferotemporal retinal nonperfusion. C) Pseudocolor fundus photo after treatment with oral trimethoprim-sulfamethoxazole and oral prednisone demonstrates resolution of the retinochoroiditis and new retinal neovascularization with vitreous hemorrhage. D) Late-phase FA demonstrates an area of RNV. E,F) Pseudocolor image and FA of RNV regression and resolved vitreous hemorrhage after scatter laser photocoagulation and intravitreal bevacizumab.

In some cases of uveitic CNV, corticosteroid and anti-VEGF treatments may have overlapping therapeutic effects.

a critical role.[17] In some cases of uveitic CNV, corticosteroid and anti-VEGF treatments may have overlapping therapeutic effects.

Multiple case studies and series have shown that uveitic CNV frequently responds to intravitreal anti-VEGF injections, often administered concomitantly with appropriate antimicrobials or with short-acting local or systemic corticosteroids where appropriate for additional effect.[13,18]

In patients with noninfectious posterior uveitis with frequent CNV recurrences, long-term immunosuppression may be useful in decreasing therapeutic dependence on anti-VEGF agents.[19]

Cystoid macular edema

The reported prevalence of uveitic CME ranges from 20 to 70 percent, and it may be more common in chronic or intermediate uveitis, and more so in adults than in children.[20]

Uveitic CME in non-infectious disease is typically treated with local and systemic corticosteroids as well as with steroid-sparing immunomodulatory therapy.[21] Oral carbonic anhydrase inhibitors and topical nonsteroidal anti-inflammatory drops may be used as adjunctive therapy.[22]

In cases of recalcitrant CME or when local or systemic toxicities limit the use of corticosteroids, the need for additional therapy arises. Patients with uveitic CME

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have increased aqueous levels of vascular endothelial growth factor compared with unaffected uveitis patients,[23] making VEGF a target of interest in uveitis.

Intravitreal anti-VEGF therapy with bevacizumab may result in an improvement in retinal thickness and visual acuity in uveitic eyes.[24–26] However, the beneficial effect is generally transient;[24] it often dissipates within a month.[27]

Patients with isolated petaloid fluorescein leakage (consistent with controlled uveitis) have a more favorable response to anti-VEGF therapy than those with more extensive ocular inflammation as evidenced by leakage of the choroid and optic nerve.[24]

Intravitreal anti-VEGF therapy with bevacizumab may improve retinal thickness and visual acuity in uveitic eyes. However, the beneficial effect is generally transient; it often dissipates within a month.

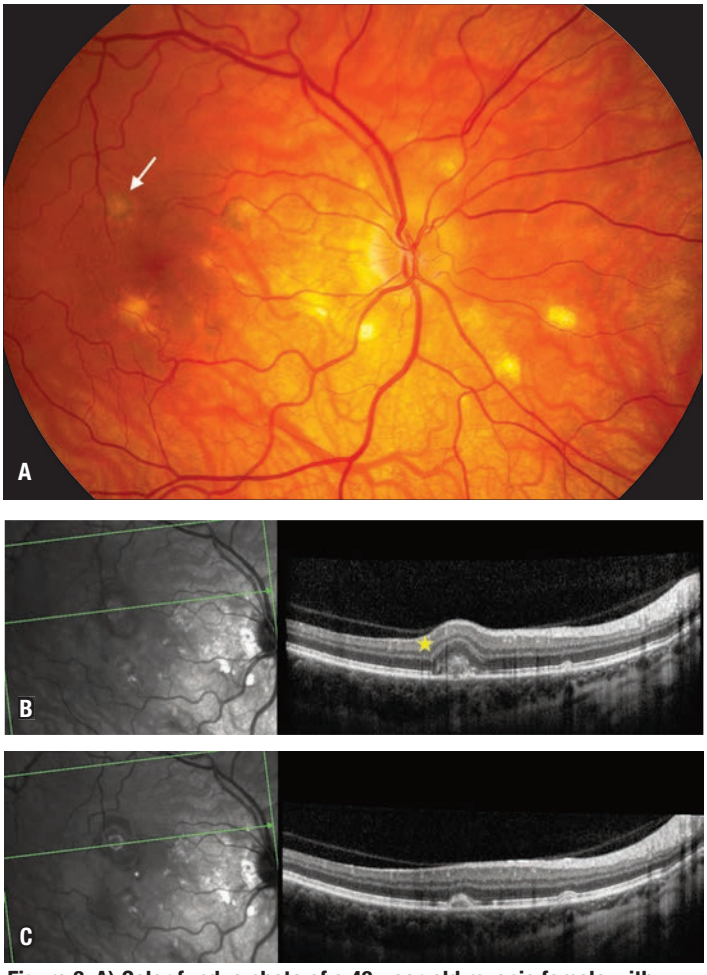

Figure 3. A) Color fundus photo of a 43-year-old myopic female with punctate inner choroiditis who noticed an increase in one of her small blind spots in the inferonasal sector, which manifested as a greenish gray subretinal lesion (arrow). B) Optical coherence tomography reveals a choroidal neovascular membrane with heterogeneous dome-shaped subretinal hyperreflective material and ellipsoid zone disruption, and a break in Bruch's layer with choroidal hypertransmission, indicating retinal pigment epithelium/photoreceptor disruption (star). C) An inactive lesion in the nasal macula. After a series of three intravitreal bevacizumab injections four weeks apart, the choroidal neovascularization became inactive and symptoms resolved.

A word of caution

Drug-induced uveitis has been reported rarely with the use of bevacizumab, ranibizumab (Lucentis, Genentech/Roche) and aflibercept (Eylea, Regeneron Pharmaceuticals), with the incidence likely in the 1 percent range.[28] However, their use is generally considered to be safe in uveitis. Brolucizumab (Beovu, Novartis) is associated with a small but significant risk of intraocular inflammation and retinal vasculitis,[29,30] and should be avoided in uveitic eyes.

Bottom line

Intravitreal anti-VEGF agents may be used successfully in select cases of uveitis with inflammatory CNV, RNV and recalcitrant uveitic CME, but the quality of

(Continued on page 25

Apellis is exploring the role of complement in Geographic Atrophy[1]

C3 is the linchpin of complement overactivation in GA.[2-7]

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Passive PFO-SO exchange

A technique for actively injecting silicone oil while passively extruding perfluorocarbon with a backflush cannula.

By Tahsin Khundkar, MD, and Sandra R. Montezuma, MD

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Bios

Dr. Khundkar is a senior vitreoretinal surgery fellow at the University of Minnesota, Minneapolis.

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Dr. Hahn is a partner at New Jersey Retina in Teaneck.

DISCLOSURES: Drs. Khundkar and Montezuma have no financial relationships to disclose. Dr. Hahn is a consultant to DORC.

Perfluorocarbon-silicone oil exchange is an important technique for minimizing the retinal slippage that can occur with PFO-air exchange during, for example, the repair of giant retinal tears, or after a relaxing retinectomy. When air comes in contact with PFO, it forms a relatively flat interface, displacing aqueous laterally and posteriorly (*Figure 1*).[1] Aqueous is able to dissect the retinal break and flow posteriorly in the subretinal space. Conversely, as SO is instilled, it's pulled down and spread out over the PFO bubble, displacing aqueous superiorly (and laterally), preventing retinal slippage (*Figure 1*).[1]

PFO-SO exchange can be achieved using a dual-active injection/extrusion mode in the vitrectomy machine.[2] Here, we highlight our preferred method of passive PFO-SO exchange, which involves actively injecting SO while passively extruding PFO with a backflush cannula (*Figure 2*).

Surgical Technique

Three-port vitrectomy and any necessary steps are performed to flatten the retina. With the vitreous cavity filled with PFO, the infusion line is removed and the SO injector is held in the empty cannula by an assistant. The surgeon actively injects SO with a foot-pedal-controlled viscous fluid injection while holding the light source in one hand and a soft-tip backflush cannula that's left open to air in the other.

Alternatively, a chandelier illuminator can be used to free up the surgeon's hand

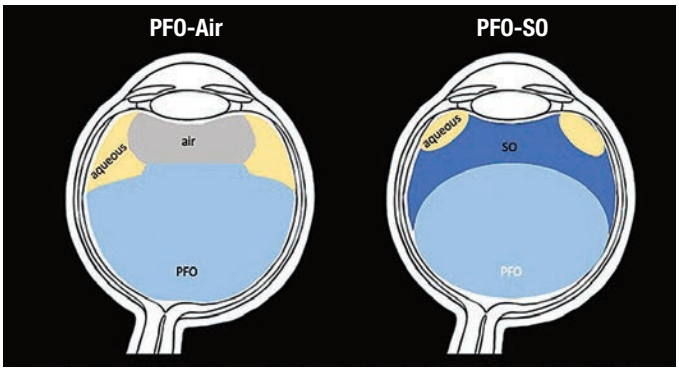

Figure 1. An air bubble has a fairly flat base when it comes in contact with perfluorocarbon, displacing aqueous laterally and posteriorly. In PFO-air exchange, this posterior trajectory of aqueous can dissect the retinal break and flow in the subretinal space. In PFO-silicone oil exchange, SO is pulled down and spread out over the PFO bubble, forming an interface that expels aqueous laterally and superiorly, thus minimizing retinal slippage. (Concept adapted from Wong D, et al. Graefe's Arch Clin Exp Ophthalmol. 1998;236:234-237. Illustrations by Tahsin Khundkar, MD)

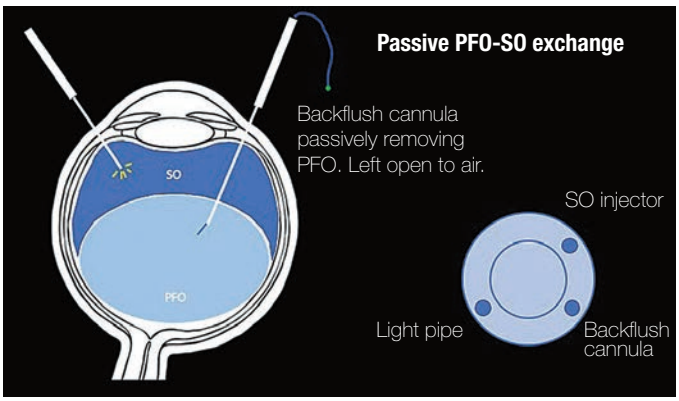

Figure 2. Schematic of the perfluorocarbon-silicone oil exchange. The surgeon holds a light source and a soft-tip backflush cannula that's left open to air. As SO is injected, the backflush cannula is maintained in the PFO meniscus and PFO is passively expelled.

View the Video

Watch as Drs. Khundkar and Montezuma perform passive PFO-SO exchange during repair of a retinal detachment. Available at https://bit.ly/VideoPearl_025

to hold the SO injector. Active injection of SO is titrated by slowing down, or stopping and waiting, based on the optic nerve perfusion or a tactile estimation of the intraocular pressure.

Initially, the backflush cannula is placed just posterior to the floating SO in order to remove the middle aqueous layer. Next, if there is residual aqueous, the cannula is directed to the edge of the retinal break. Finally, once the SO meniscus passes the posterior edge of the retinal break, the backflush cannula is redirected to the optic nerve to remove the remaining PFO.

Why use passive aspiration?

An advantage of passive aspiration is that the surgeon doesn't have to change any parameters in the vitrectomy machine or prime infusion tubing. While this is particularly useful in certain cases, such as when trying to prevent dislodgement of a retinal free-flap during closure of a refractory macular hole,[3] this technique can be used in any case in which SO is planned.

We encourage you to practice this technique regularly to become familiar with it. RS

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Using anti-VEGF agents in uveitis

(Continued from page 22)

evidence supporting their efficacy is low,[1] so decisions must often be made based on limited evidence and clinical judgment.

When considering anti-VEGF treatment in uveitis, concomitant treatment to control the underlying inflammatory or infectious disease is critical. In uveitic eyes with RNV, consider laser photocoagulation to areas of ischemic retina with adjunctive anti-VEGF therapy for residual neovascularization.

While no studies provide guidance on the choice of specific anti-VEGF agents in uveitis, brolucizumab should likely be avoided in inflamed eyes due to its increased risk of intraocular inflammation and occlusive retinal vasculitis. RS

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Who's predisposed to anti-VEGF-induced IOI?

What clinical trials and postmarket data reveal about intraocular inflammation risk with brolucizumab.

By Huy Nguyen, MD, and Michael Singer, MD

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Bios

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Dr. Singer disclosed relationships with Aerie Pharmaceuticals, Allegro Ophthalmics, Allergan/AbbVie, EyePoint Pharmaceuticals, Genentech/Roche, Kodiak Sciences, Mallinckrodt, Novartis, Regeneron Pharmaceuticals, Santen Pharmaceutical, Spark Therapeutics, Icon, Ionis Pharmaceuticals, Kalvista, Opthea, Optos, Senju and Sydnexis.

Take-home points

- The higher incidence of intraocular inflammation and potentially more severe sequelae leading to vasculitis, along with occlusive vasculitis with retinal vascular occlusion and irreversible visual loss, is unique to brolucizumab.
- More of the patients receiving brolucizumab in HAWK/HARRIER who developed IOI actually gained letters by the end of the study, but the vast majority who developed vasculitis and or vascular occlusion lost the most vision.
- Treatment-naïve patients had no reported cases of occlusive vasculopathy after the first injection of brolucizumab.
- Topical steroids are a reasonable treatment for isolated anterior chamber inflammation, but intermediate or posterior segment inflammation may require more aggressive intervention.

As we all know, anti-VEGF medications have transformed how we care for multiple retinal pathologies. However, the treatment schedule for each anti-VEGF medication varies based on its duration of action, disease activity and treat-and-extend schedule with individual patients, especially for neovascular age-related macular degeneration. The finite window of efficacy per injection creates a revolving door of injections for each affected eye. And refractory cases of diabetic macular edema and nAMD may accelerate the revolving door with the need for trial-and-error of various anti-VEGF agents, with or without adjunctive ocular steroids.

The marketplace has responded to these clear demands with progressively more potent anti-VEGF candidates with longer durations of action. However, brolucizumab (Beovu, Novartis) has been heavily scrutinized due to its higher reported incidence of mild to severe intraocular inflammation despite its potent "drying" effects and longer duration.

While brolucizumab finds its niche in the treatment arsenal in addressing refractory cases of nAMD, the question remains: What patients are at highest risk of suffering visually significant IOI? Answering this question can help to triage appropriate candidates and guide development of potentially safer intravitreal anti-VEGF formulations. We tackle that question here.

Early reports of IOI

IOI has been marked as an adverse event of interest since the VIEW study, which identified an incidence of 0.005 to 1.5 percent in patients receiving intravitreal ranibizumab (Lucentis, Genentech/Roche) and 0.5 to 1.1 percent with intravitreal aflibercept (Eylea, Regeneron Pharmaceuticals).[1] The higher incidence of IOI in 6-mg brolucizumab (4.6 percent in HAWK and HARRIER), and potentially more severe sequelae leading to vasculitis (3.3 percent) and occlusive vasculitis with retinal vascular oc-

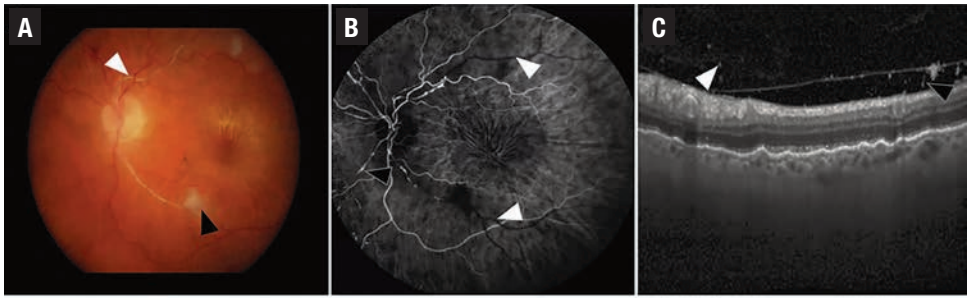

Figure 1. In a case of iridocyclitis and retinal arterial thrombosis from HAWK and HARRIER, A) color fundus photography demonstrates whitening of the retinal artery consistent with retinal artery occlusion (white arrowhead) and a cotton wool spot (black arrowhead). B) Fluorescein angiogram in the venous phase demonstrates nonperfusion of the retinal arteries (white arrowheads) and arterial box-carring (black arrowhead). C) Spectral-domain optical coherence tomography demonstrates cells in the vitreous on the posterior hyaloid. (*Source: Singer M, et al. Ophthalmol Retina. Published online May 8, 2021: doi.org/10/1016/j.oret.2021.05.003.*)

clusion (2.1 percent) and irreversible vision loss is unique to the agent (*Figures 1 and 2*).[2]

Two groups have examined this adverse effect in depth since brolucizumab launched in October 2019: the Research and Safety in Therapeutics (ReST) panel established by the American Society of Retina Specialists; and Novartis' own safety review committee, an independent group of experts charged to investigate reported cases of IOI in HAWK and HARRIER. The two groups were tasked to determine any trends that might elucidate the underlying cause.

The two groups' conclusions are congruent and ultimately recommend use of brolucizumab only in patients who have had a careful examination to rule out active intraocular inflammation.[1,2] We compared postmarket data with HAWK and HARRIER post-hoc analyses to contextualize potential etiologies and risk factors for IOI after anti-VEGF injections.

Drilling down into HAWK and HARRIER

HAWK and HARRIER were Phase III clinical trials designed to determine the efficacy of brolucizumab (3 mg and 6 mg in HAWK, 6 mg in HARRIER) in treating nAMD relative to aflibercept 2 mg.[3] Enrolled patients were treatment-naïve and received baseline fluorescein angiography and spectral-domain optical coherence tomography before starting three monthly

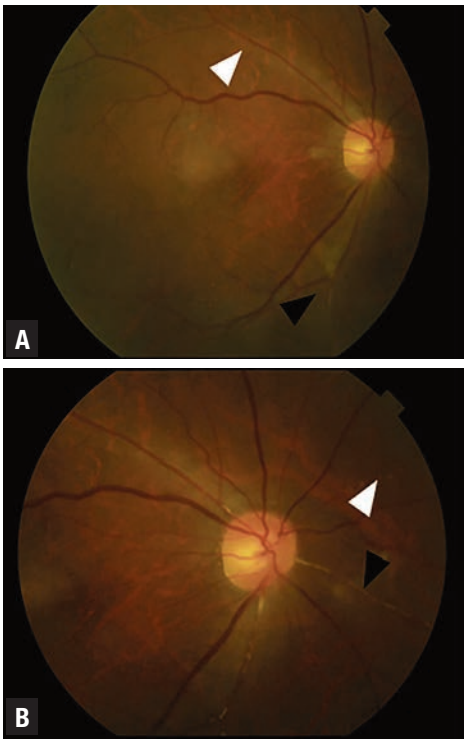

Figure 2. A case of uveitis and retinal artery occlusion from HAWK and HARRIER. Color fundus photographs show small and focal narrowing of retinal arterioles (white arrowheads) and occlusion (black arrowheads). (*Source: Singer M, et al. Ophthalmol Retina. Published online May 8, 2021: doi.org/10/1016/j.oret.2021.05.003.*)

Two expert groups ultimately recommend use of brolucizumab only in patients who have had a careful examination to rule out active intraocular inflammation.

loading doses. Brolucizumab recipients were then evaluated and, if they qualified, maintained on q12-week dosing but changed to q8-week dosing if OCT and vision criteria showed evidence of disease activity.

Slightly more than half of the patients in the brolucizumab arms continued on the q12-week dosing within the first year. In terms of AEs, 49 of the 1,088 eyes treated with brolucizumab had at least one IOI AE at a mean time of occurrence at 100 days, and 18 days from the last injection.[4] Eighty-seven percent were treated with topical steroids and others were observed or treated with oral or intraocular steroids.

Among the patients treated for IOI, 80 percent achieved resolution, 10 percent did so with sequelae and 10 didn't show any resolution. Thirty-six eyes with one prior IOI event continued on brolucizumab, of which 12 suffered another IOI event and discontinued the study.

The unique AE of IOI and occlusive vasculitis occurred in 2.1 percent of eyes, of which five of seven eyes (71 percent) resulted in vision loss of ≥15 letters. The overall impact of IOI AEs on vision was a maximum loss of 16.31 EDTRS letters within three months of the culprit injection, a loss of 0.22 letters when tracked to the end of study.[2]

It's interesting to note that among patients who developed IOI, more gained letters by the end of the study, but the vast majority who developed vasculitis and or vascular occlusion lost the most vision. The post-hoc analyses didn't compare IOI between aflibercept and brolucizumab, but noted that aflibercept had less than a 1-percent incidence of IOI; all cases were mild or moderate in severity.

It's interesting to note that among patients who developed intraocular inflammation, more gained letters by the end of the study, but the vast majority who developed vasculitis and/or vascular occlusion lost the most vision.

Postmarket data

The reported incidence of IOI in postmarket data from Novartis has fluctuated from greater than to less than that of HAWK and HARRIER. By March 2020, approximately 65,000 to 70,000 injections had been given to 37,000 eyes with vasculopathies noted in 26 eyes of 25 patients.[4] The reported incidence of occlusive vasculitis as of August 2020 was 4.71 per 10,000 injections, usually in the presence of IOI.[1]

Although data are still evolving, the occlusive vasculopathy incidence per injection in HAWK/HARRIER is still three times the rate in postmarket data, which suggests underreporting. One reason could be the difficulty differentiating occlusive vasculopathy in the presence of IOI from postinjection endophthalmitis, which also presents at a rare incidence of 0.02 percent.[5]

Smaller real-world studies for nAMD (non-treatment-naïve patients, n=152) have also reported incidences of elevated ranges of brolucizumab-induced inflammation at 8.1 percent for IOI, 0.6 percent for occlusive vasculitis, and 1.2 percent for severe vision decline in IOI eyes.[6]

The Komodo Health Database and IRIS registry have reported postmarket IOI incidence of 2.4 percent with vasculitis and occlusion incidence of 0.55 percent. Their multivariate regressions revealed a 4.5-percent risk of an occlusive event within the first six months of a prior IOI event (eight times baseline risk) and 10-percent risk of repeat IOI (four times baseline risk).[7]

MERLIN (NCT03710564, n=529) was a clinical trial that compared brolucizumab 6 mg q4-week to aflibercept 2 mg q4-week in previously treated patients that have persistent retinal fluid. Data as of July reported the incidence of IOI, vasculitis and occlusion in brolucizumab vs. aflibercept at 9.3 vs 4.5 percent, 0.8 vs 0 percent and 2 vs 0 percent. As a result the trial was halted.[8]

KITE (NCT03481660, n=361) and KESTREL (NCT 03481634, n=571), parallel studies targeting the DME population as HAWK and HARRIER did for those with nAMD, also compared brolucizumab 3 and 6 mg and aflibercept 2 mg (KESTREL) or brolucizumab 6 mg and aflibercept 2 mg (KITE). The brolucizumab arms had q6-week interval loading doses before continuing on a q8- to q12-week regimen. The

Risk factors for IOI and how to manage it

Several clues hint at a delayed hypersensitivity event in cases of intraocular inflammation after injection of brolucizumab. HAWK/HARRIER showed the duration between prior injection and adverse event is 25.5 days on average (highly variable range), with most occurring between three to six months after the first injection.[3] No cases of occlusive vasculopathy after the first injection were reported in treatment-naïve patients.

Of the 36 eyes that had an initial intraocular inflammatory event and continued treatment, 12 had a second adverse event. A basal incidence of 4.6 percent argues against such an unlucky independent recurrence. Interestingly, 36 to 52 percent of patients had anti-brolucizumab antibodies even before the study started, and approximately one-quarter had boosted or new titers by study end. Patients with titers had a 6-percent incidence of IOI vs 2 percent in those without.[10] Ana Bety Enriquez, MD, and colleagues and the Komodo registry identified female gender as an additional risk factor.[6,7]

Those risk factors drive general recommendations and contraindications for brolucizumab. In using the potent agent for patients with refractory progressive vision loss, patients should be aware of the known risk of IOI so far. Poor candidates are those with prior IOI or monocular patients. Brolucizumab is contraindicated in patients with active IOI.

A careful dilated examination and return precautions should be performed before injection. For isolated anterior chamber inflammation, a widefield fluorescein angiogram, optical coherence tomography and treatment with topical steroids are reasonable. More aggressive intervention with systemic medications or intravitreal injection should be considered for intermediate or posterior segment involvement. Outcomes for vitrectomy haven't revealed a benefit on visual acuity, but data so far data are scarce and skewed toward more severe IOI cases. So the decision remains up to individual discretion.[11]

—H.N., M.S.

spaced out loading doses for brolucizumab revealed IOI, vasculitis and occlusion rates vs. aflibercept (q4-week loading doses) of 1.7 to 4.7 percent vs. 0.5 to 1.7 percent, 0 to 1.6 percent vs. 0 percent, and 0.5 to 1.1 percent vs. 0.3 to 0.6 percent, respectively.[9]

Bottom line

The association between brolucizumab and a heightened risk of IOI compared with other currently available anti-VEGF agents has been widely reported. Data from clinical trials and postmarket analyses have provided more information about who's at greatest risk of IOI with brolucizumab, and the agent is contraindicated in patients with a history of IOI. Topical steroids are a reasonable first-line treatment for cases of anti-VEGF-induced IOI. RS

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Brolucizumab is contraindicated in patients with a history of intraocular inflammation. Topical steroids are a reasonable first-line treatment for cases of anti-VEGF-induced IOI.

Treat and extend: An international view

Three experts from Canada, Switzerland and Israel provide insights into the nuances of adherence, treatment intervals and emerging therapies.

By Justus G. Garweg, MD, Peter J. Kertes, MD, FRCSC, and Anat Loewenstein, MD

Take-home points

- Patients appreciate the predictability of regular treatment intervals of treat and extend.
- Patients with myopic choroidal neovascularization or a secondary CNV uveitis may not be suitable for a treat-and-extend regimen.
- Careful follow-up with patients who miss appointments and flexible scheduling are keys to adherence.
- New agents with greater durability will require rethinking of T&E intervals.

Treat-and-extend has emerged as the preferred method for treating neovascular age-related macular degeneration with anti-VEGF drugs. Here, three internationally recognized experts on T&E—Anat Loewenstein, MD, of Tel Aviv, Israel; Peter Kertes, MD, of the University of Toronto and lead author of the landmark CANTREAT study; and Justus Garweg, MD, of Bern, Switzerland, and one of the international EyeCOPE study investigators—share their thoughts on clinical trial guidance, what types of patients are best suited to T&E, and the potential impact of emerging therapies that would enable even longer treatment intervals.

Q ***What can retina specialists take away from the clinical trials and apply in the clinic when it comes to treat-and-extend?***

No tolerance for intraretinal fluid

Dr. Garweg: Luckily, the majority of patients respond well to anti-VEGF therapy, whichever drug you choose. So the drug choice is critical mainly for patients with advanced disease and poor responders, whom you don't know beforehand. But clearly, if the patients already have macular destruction at diagnosis, then they are not likely to have significant visual gains. If there's already subretinal fibrovascular tissue and the ellipsoid zone is destroyed, then whatever you do may stabilize but not improve vision.

What we've learned in real life is to tell our patients that we cannot predict how much vision they will gain. After the three-injection loading phase, we can then see how a patient has gained vision. The aim would be the long term, which means maintaining the visual gain that was reached by the end of the loading phase for five years or more.

Bios

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Anat Loewenstein, MD, is chair of the ophthalmology division at Tel Aviv Medical Center and professor of ophthalmology, incumbent of the Sydney A. Fox Chair in ophthalmology, and vice dean at Tel Aviv University. **DISCLOSURES: Dr. Loewenstein** reports financial relationships with Allergan/AbbVie, Bayer, Beyeonics, Novartis, Notal Vision, Roche and WebMD.

Peter J. Kertes, MD, FRCSC, is the former chief of ophthalmology and a vitreoretinal surgeon at Sunnybrook Health Science Centre and professor of ophthalmology at the University of Toronto. He is the principal investigator of the Canadian Treat-and-Extend Analysis Trial with Ranibizumab (CANTREAT). **DISCLOSURES: Dr. Kertes** disclosed relationships with Bayer, Allergan, Novartis, Alcon and Novelty Nobility, and owns stock in Arctic Dx.

One of the important learnings involves the appearance of the macula. It can look quite damaged, and you can be surprised at how much vision it gains. Therefore we should know about the patients' visual expectations before initiating treatment, as patients have to learn that it's not always granted that they'll achieve reading or driving vision, even under consequent treatment. Predicting treatment outcomes is very important for long-term patient compliance.

Adherence to the treatment protocol is the one key issue that leads to good long-term outcomes. And we have learned that intraretinal fluid shouldn't be tolerated. This is at the discretion of the treating physician, but if the macula isn't significantly drier after six months and not dry after 12 months, then we would want to switch the agent.

Patients appreciate predictability

Dr. Kertes: AMD is a heterogeneous disease and patients have different responses to treatment. A treat-and-extend regimen allows us to pair a patient's treatment needs with their treatment frequency. It allows them to retain their vision as long as possible, and I think it improves compliance.

My sense is that patients like knowing beforehand that they're getting an injection, as opposed to a *pro re nata* regimen, when patients don't know if they're going to need an injection before the visit. There's some peace that comes from knowing what's going to happen when they go to see a doctor.

The COVID-19 pandemic has really highlighted the value of the treat-and-extend regimen, so we can see patients less often. If they have an established treatment interval, we can get them in and out relatively quickly and not expose them to any undue risk.

Extending by two or four weeks

Dr. Loewenstein: There aren't many trials that were done regarding the treat-and-extend regimen. The main one is the ALTAIR[1] trial; also the ARIES trial looked at early and late treat-and-extend.[2] Some small studies had been conducted in Spain. There aren't a lot of prospective, level I data, but from the existing data, it seems that the treat-and-extend regimen is as effective as the PRN treatment with fewer non-injection visits. Theoretically, I think we can conclude that using treat-and-extend is a feasible regimen.

The other thing that we can conclude from the trials is, that we can consider extending some injections by four weeks rather than by two weeks. This is based on the ALTAIR study, in which both of the study arms reported similar results whether the injections were extended to two-week or to four-week intervals. However, I think that in clinical practice, most of us are using an extended regimen of two weeks.

We can also conclude from the trials that the treat-and-extend regimen is beneficial both for aflibercept and ranibizumab. This is an important finding, and I think it's obvious to everyone that it decreases the patient's burden and still maintains the visual acuity outcome by avoiding non-injection visits.

Another lesson that we can learn from the trials, specifically the ARIES trial,[2] is that it's more beneficial to start treat-and-extend early in the course of the process. You don't have to maintain a year of fixed regimen and only then initiate a treat-and-extend approach.

Q ***What type of patient is best-suited for a T&E regimen?***

nAMD patients only

Dr. Kertes: Neovascular AMD is especially well-suited for treat-and-extend. We know these patients for the most part will need to be treated long-term, unlike the other indications for anti-VEGF agents such as diabetic macular edema or vein occlusions. Many of those patients don't need treatment in perpetuity, although some do. Whereas AMD patients really do generally need treatment long-term.

As we get agents that last longer and longer—as we get more and more durable agents—we'll be able to establish very reasonable, very long treatment intervals that I think will be very well tolerated by patients and their caregivers, and make our lives and clinics a little less crazy.

Sometimes PRN first

Dr. Loewenstein: For me, every type of patient is suited for a treat-and-extend regimen. I find it difficult to explain the treat-and-extend regimen to patients that were initially treated with a PRN regimen, so a switch is difficult. The reason is that patients, once I educate them that when intraretinal fluid appears they need an injection, don't really understand why they need to be injected when they don't have any fluid.

Other than that, for me treat-and-extend is the best way to go. We usually do a loading phase of three injections. Usually we have to start with bevacizumab, and then once we determine that it doesn't work, we can move to one of the registered drugs. Sometimes I try a PRN regimen first just to give the patients a chance; maybe they're in the

group that doesn't need so many injections. But most of the time, I go straight a to treat-and-extend approach. I actually offer patients both options, but for me the preference is to go ahead with the treat-and-extend regimen.

I will attempt a PRN regimen first, if this is the patient's choice, mainly if there's an early lesion. Some patients need only a few injections; though it's not common. I will give one PRN injection to see if the patient can go without injections for a longer period of time. But I only give them one chance. When they need to be injected the first time, I go to the treat-and-extend regimen.

Exceptions to any AMD patient

Dr. Garweg: Any patient with macular neovascularization may undergo a treat-and-extend protocol, with some exceptions: patients with myopic choroidal neovascularization, for example, or with a secondary CNV in uveitis.

Formerly we would extend to 12 weeks, but nowadays we routinely extend to 16 weeks, and in some cases even to 20 weeks without interim follow-up. If patients are completely stable, as we have shown in a recent publication, then we might discuss pausing treatment.[3]

I don't say stop treatment. If we pause treatment, then we go for two months with controls. Many of our patients prefer to go on with continuous treatment every 14 to 16 weeks compared to having a consult every eight weeks and not knowing what to expect.

The advantage of being consequently under-treated isn't that you avoid recurrences. However, even if recurrences do occur, they do so with less vision loss and a lower risk of macular hemorrhages than they would otherwise.

If you stop treatment and the patient has a recurrence, then there's a distinct risk of macular hemorrhage. I think patients with an only eye and those in whom the fellow eye is already scarred would benefit from going on with this treatment, just for the safety considerations.

Q Are there any lessons from the COVID-19 pandemic for keeping T&E patients adherent to follow-up and monitoring?

Remote clinic, home visits

Dr. Loewenstein: During the pandemic, we called patients and made sure that we were providing them with a safe environment. Also, in our clinic we were very lucky because we had a remote clinic outside of the hospital where we could perform injections and evaluations, which was very beneficial for the patients.

Moreover, we reached out to patients at home. If patients were in the loading phase or had an optical coherence tomography scan done elsewhere, we even performed the injections in their homes. We don't have the resources to do that now, but we do go out and inject in elderly home shelters for patients who are reluctant to come to the clinic. However, we don't have a suitable system and the resources to call every patient that didn't come in to be examined.

Flexibility on missed visits

Dr. Garweg: AMD patients can be prone to forgetting their appointments. So, we have to fit the appointments in not with only the patients, but also with their relatives. And we have to fit in new appointments if a patient forgot about the scheduled meeting. We have a nurse who specifically cares for patients who aren't showing up. She calls them and arranges for new appointments so that every patient has a chance to get the treatment they need.

It's worth adding that patients who come with a new diagnosis of exudative AMD are very unhappy and they have no idea about treatment. They expect that they get one injection and the problem is solved, like with a cataract; you get cataract surgery and the problem is solved.

They have to learn that they have a chronic disease, and the treatment plan is very high in the beginning, but that it lessens over time. In the majority of cases, they will get along with three-and-a-half to four injections in years three, four and five, and so on, but in single cases, many more injections might be needed to maintain vision.

It's also important that you meet patient expectations in terms of functional gains or functional needs. For example, if you have a patient who has a significant increase in his vision but aims at reaching a driving vision and fails to do so, this patient will be unhappy. So, you have to first educate the patient—what they have to expect. But you also have to learn what the patients expect from their treatment, and you have to bring them back to a realistic level in order to maintain treatment adherence.

Quick follow-up, longer intervals

Dr. Kertes: As the intervals between treatments become longer, the risk of patients missing their appointments becomes greater. But there are many ways to engage them. There are patients who do forget and need to be reminded of their appointments, so my staff can call them and remind them.

If they do miss an appointment, we follow up carefully, make sure they're well, and give them another appointment very soon. During the pandemic there were patients that wouldn't even come into the hospital, with the uncertainty and the fear of the pandemic looming. Patients certainly did fall off the wagon and miss their appointments but, fortunately, most of those patients did OK and were able to regain whatever vision was lost.

Sometimes we were able to establish a longer interval because they missed appointments due to COVID-19, but a small number came back with severe vision loss that we haven't been able to recover. We're lucky as ophthalmologists; our patients really do value their vision—particularly a patient who's lost vision in one eye and needs treatment in their fellow eye. They're pretty diligent. They want to get their eyes treated. They don't want to risk losing vision.

Q ***Any closing thoughts?***

Managing high-treatment cases

Dr. Garweg: Two-thirds of the cases end up with a low treatment burden, which is every 12 to 16 weeks. One-third of cases have a high treatment demand. These are the more critical cases because they have chronic, slowly progressive active disease. If they don't comply with treatment, then they usually have severe lesions over three to five years. Those are the cases where we consequently switch to another drug.

If you have a low responder in one eye, that doesn't necessarily predict low response or poor response in the fellow eye. If it's treated early, then the risk for poor response is low. If you catch an eye late or with very prominent scarring, then the risk for poor response is higher, but even then, consequently switching is very important. Also, this gives patients the notion that you'll try anything to maintain their vision, which, again, supports their compliance.

Monthly injections are not failures

Dr. Kertes: This is obviously an active area of investigation. There are a variety of different strategies that have been developed and different agents that are in clinical trials. Most of these agents are tested in a fixed-dosing regimen and are compared to monthly or bimonthly injections, so to assess the real durability and efficacy of an agent, it's a little bit disingenuous to compare our current agents and how they've been approved on label with regular frequent intervals. Every agent will stand on its own merits based on how well it performs in a treat-and-extend regimen, which obviously takes time and usually happens post-approval; but those are the more relevant comparisons.

With newer agents and longer durations, it's realistic to expect that many of our patients will need maybe as few as one or two injections a year and be able to maintain their vision. I think most patients and caregivers and practitioners can tolerate that. I think that's much more manageable than monthly or every two-month injections.

Keep in mind that there are patients who need more frequent injections. As difficult as that is, we found many of those patients in the CANTREAT study who needed monthly injections maintained good vision.[4,5] I think there's a tendency for us to think of those patients as treatment failures, but they're not. They're just patients that need more anti-VEGF than others. We should pair our treatments with the patients' needs to maintain them at the best vision that we can.

Adopting emerging agents

Dr. Loewenstein: We will need to change the way we treat patients with some of the newer drugs that can extend treatments out to three and four months. I think if you need to perform an injection every three or four months, you might not need a treat-and-extend regimen. Although, maybe you would because if you can extend to three or four months, maybe you could go out to three-and-a-half months, maybe four-and-a-half months.

Also, the new emerging technology of the Port Delivery System containing ranibizumab requires a refill only once every six months. The port is not something that I would want to extend. I would like to see my patients at least once in six months. RS

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Understanding the risks of systemic vascular disease

The retina is the canary in the coal mine for evaluating future systemic vascular disease in people with diabetes.

Bobeck S. Modjtahedi, MD

By Bobeck Modjtahedi, MD

Take-home points

- Patients with diabetes who may seem to have their disease under good control can still develop significant macrovascular disease over short-term follow-up.
- Aggressive medical management has been shown to substantially improve vascular outcomes in high-risk patients. Retinal images may improve our ability to stratify at-risk patients to deliver better care.
- Higher degrees of retinopathy confer a higher risk of future systemic vascular disease.
- Artificial intelligence may make it easier to better evaluate future disease risks.

One of the aspects of being a retina specialist that attracted many of us to this field was the ability to stay connected to patients' systemic conditions. Usually this takes the form of managing the retinal complications of systemic disease. However, emerging research increasingly suggests that the retina may hold promise in the evaluation and management of extraocular conditions.

We have the opportunity to form long-term relationships with our patients, and part of that entails seeing their general health evolve. Among people with diabetes, for example, it's not unusual for us to witness the progression of their diabetic disease over the years. Frequently, patients who may seem outwardly fine but whose retinas demonstrate advanced retinopathy will deteriorate clinically. Their retinal status is clearly a harbinger of things to come. Within a few years these patients are often on dialysis or suffer significant macrovascular events such as myocardial infarctions or cerebrovascular accidents.

The question then becomes, what role can we as retina specialists play in the broader medical management of our patients? This has been an area of considerable interest for many years, with research having focused on the relationship between retinal status and several conditions including cardiovascular, renal and cerebrovascular diseases, and Alzheimer's disease.[1-4]

Stratifying heart disease risk

Using retinal images to stratify systemic vascular disease risk is appealing because it has been well established that aggressive medical management in high-risk patients can substantially reduce their risk of MI and CVA. There's a strong scientific rationale for using retinal images for vascular disease stratification since the retina is the only place where blood vessels can be visualized directly.

We additionally know histologic similarities exist between the retina and brain, given their shared embryotic origin.[3] Some authors, such as Jack W.R. Brownrigg, MRCS,

Bio

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DISCLOSURE: Dr. Modjtahedi reported receiving research support from Genentech.

and colleagues in the United Kingdom, have found that accounting for microvascular complications of diabetes would cause 20 percent of diabetes patients to move into a different cardiovascular risk category.[5]

Several risk calculators have been used to determine the future risk of cardiovascular disease and help guide management decisions, such as when to start aspirin or statin therapy.

One such commonly used tool is the American College of Cardiology/American Heart Association atherosclerotic cardiovascular disease calculator.[6] It uses age, gender, race, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, history of diabetes, smoking status, hypertension treatment, statin use and aspirin use to provide a 10-year risk estimate for patients. Although these risk calculators provide important insights into disease management, their real-world performance can sometimes be lacking because they may miscalculate true risk.[7]

DR as a biomarker of systemic vascular disease

Using the retina as a window into a patient's cardio- and cerebrovascular disease status is attractive because it is relatively easy to view, especially when compared to other tools such as cardiac calcium scores.

Several studies have evaluated whether diabetic retinopathy was independently associated with cardiovascular outcomes, but they produced mixed results. The cause of these conflicting findings are multifactorial and relate to how the studies measured outcomes, length of follow-up, covariates and cohort size.

Additionally, many studies categorized patients simply as retinopathy vs. no retinopathy, which may not have provided enough granular detail to find important associations. With this in mind, we attempted to answer some of the questions around whether diabetic retinopathy is an independent risk factor for systemic vascular disease.[1]

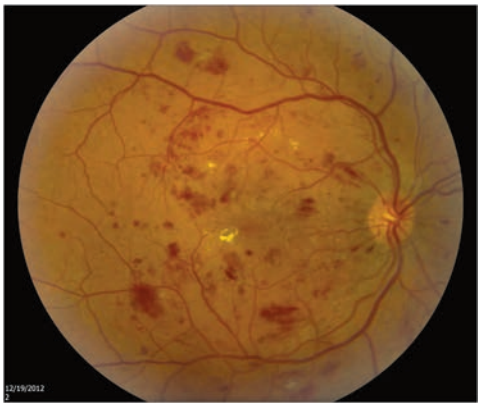

Figure 1. Moderate nonproliferative diabetic retinopathy, shown here with macular edema, was found to carry a 92 percent greater risk for myocardial infarction and a 90 percent greater risk for development of congestive heart failure. (*Courtesy Nidhi Relhan Batra, MD*)

Quantifying vascular disease risk

Our study analyzed the five-year outcomes of patients who received DR screening in our telemedicine program. We graded retinopathy severity based on 45-degree fundus photos, with the highest degree of retinopathy between the two eyes chosen for analysis. We divided severity into four categories: no retinopathy; minimal nonproliferative diabetic retinopathy; moderate-to-severe NPDR (*Figure 1*); and proliferative diabetic retinopathy (*Figure 2, page 36*).

We then calculated the five-year risk of new MI, congestive heart failure (CHF), CVA and all-cause mortality after adjusting for key cardiovascular and diabetes risk factors that included gender, age, race or ethnicity, diabetes duration, hemoglobin A1c, LDL and HDL levels, tobacco use, history of hypertension, systolic blood pressure, diastolic blood pressure, body-mass index, statin use, estimated glomerular filtration rate and urine microalbumin-to-creatinine ratio.

We were able to use a large real-world population that allowed for sufficient statistical power to detect differences between groups (n=77,376). The results showed that even after accounting for the aforementioned covariates, DR severity was signifi-

Although several cardiovascular risk calculators can provide important insights into disease management, their real-world performance can sometimes be lacking, as they may misestimate true risk.

cantly associated with the risk of all the outcomes considered, with higher degrees of retinopathy appearing to carry an increased risk for each outcome.

The increased risk of each outcome with increasing retinopathy severity was especially noteworthy. When comparing patients with DR and those with no retinopathy, we observed the following relationships in terms of hazard ratio and range:

- ***Minimal NPDR:*** MI (HR, 1.30; 95% confidence interval [CI], 1.15-1.46); CHF (HR, 1.29; 95% CI, 1.19-1.40); CVA (HR, 1.31; 95% CI, 1.18-1.46); and all-cause mortality (HR, 1.15; 95% CI, 1.05-1.25).
- ***Moderate-to-severe NPDR:*** MI (HR, 1.92; 95% CI, 1.57-2.34); CHF (HR, 1.90; 95% CI, 1.66-2.18); CVA (HR, 1.56; 95% CI, 1.29-1.89); and all-cause mortality (HR, 1.55; 95% CI, 1.32-1.82).
- ***PDR:*** MI (HR, 1.89; 95% CI, 1.26-2.83); CHF (HR, 1.96; 95% CI, 1.47-2.59); CVA (HR, 2.53; 95% CI, 1.84-3.48); and all-cause mortality (HR, 1.87; 95% CI, 1.36-2.56).

These results point to a striking trend, as illustrated in Figure 3. For example, a patient with PDR has a 253 percent higher risk for a CVA in the next five years than a person with diabetes but without retinopathy, even after controlling for risk factors such as HbA1c or blood pressure.

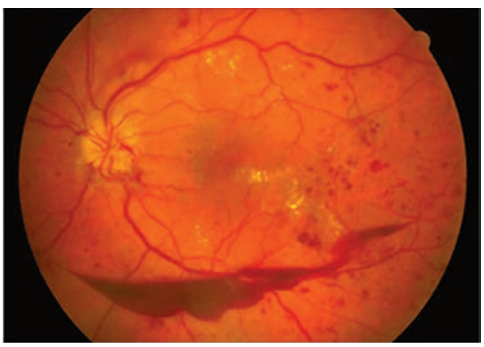

Figure 2. Proliferative diabetic retinopathy, shown here with a preretinal hemorrhage, was found to carry an 89 percent greater risk for myocardial infarction and a 253 percent higher risk for cerebrovascular accident. (*Courtesy Nidhi Relhan Batra, MD*)

Importantly the patients who participated in this study were part of a DR screening program and typically not already under the care of an ophthalmologist. As a result, the number of patients with more advanced forms of severe retinopathy, who were by extension also generally "sicker," were under-represented in this cohort. This may have ultimately resulted in an underestimation of systemic disease risk in patients with higher degrees of retinopathy.

In line with clinical experience

These findings are consistent with many of our clinical experiences. I've had many patients whose lab values seemed at target goals, but whose retinas showed significant retinopathy. These patients ultimately suffered a MI or CVA within a few years of establishing care with me. The reason for this may be that the retina provides a more holistic view of a patient's vascular disease burden.

While current risk calculators are limited in the number of variables they can consider and are typically constrained to the most recent set of values, the retina may provide us with a view of the aggregate damage to the vascular system over years—including prior years of worse diabetes control—and provide a superior biomarker for future disease.

Potential for technology, AI

Several advances in technology may provide even more insights. Greater retinal visualization with widefield viewing systems and more detailed visualization of the retinal vasculature with optical coherence tomography angiography allow for better characterization of retinal changes.

Artificial intelligence/machine learning may hold promise in using retinal information for risk stratification. Subtle retinal changes may be easier to quantify using AI which may also allow for more detailed analysis than is practical by a human grader.

While human grading is currently limited to traditional classification schemes (such as microaneurysm and dot-blot hemorrhages), AI-based solutions may find new markers of systemic disease that we humans may not even be considering. Tyler Hyungtaek Rim, MD, and colleagues in Singapore and South Korea recently

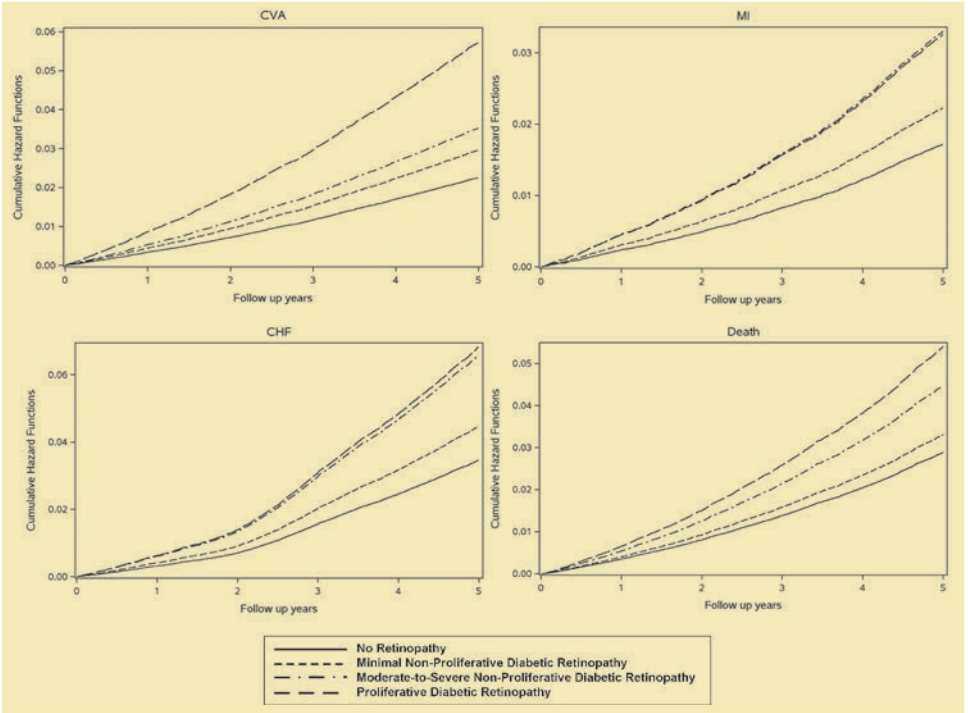

Figure 3. Cumulative hazard functions for cerebrovascular accident (CVA), myocardial infarction (MI), congestive heart failure (CHF) and all-cause mortality by diabetic retinopathy status. These results show that diabetes patients with moderate-to-severe nonproliferative diabetic retinopathy and proliferative DR are at significantly higher risk for a cardiovascular event than diabetes counterparts with no retinopathy or minimal NPDR. (*Reprinted with permission Ophthalmology.*[1])

demonstrated that a deep-learning-based analysis of retinal images was comparable to CT-scan measured cardiac calcium score in predicting cardiovascular events.[8]

Bottom line

I think the findings of our publication are noteworthy because they demonstrated such a strong relationship existed even when using "limited" retinal evaluation (two 45 degree photographs per eye without the use of widefield photographs or angiography) and "primitive" grading schemes (human-graded degree of retinopathy as opposed to an AI-based solution). This gives us hope that more advanced imaging and interpretation schemes may undercover even more powerful relationships.

In the future we may use the retina like a vital sign that helps optimize the medical management of our patients for a host of diseases, not only systemic vascular disease. RS

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In the future we may use the retina like a vital sign that helps optimize the medical management of our patients for a host of diseases, not only systemic vascular disease.

Making the retina workplace more ergonomically friendly

How a few modifications in the clinic and OR—and perhaps some yoga—can help overcome occupational aches and pains.

Sunir Garg, MD, FACS

By Sunir Garg, MD, FACS

Take-home points

- Ophthalmologists have a higher risk of occupational injury than other physicians; the main reasons are poor posture, repetitive motions and the fact that we repeatedly maintain awkward positions.
- Our workflow isn't designed for the long-term health of our bodies, but there are a number of simple, inexpensive modifications we can make to help reduce injury.
- At the slit lamp, something as simple as lifting the footrest can allow you to move closer to the patient and sit more upright.
- Yoga and other ways of improving one's flexibility—Pilates, physical therapy, massage and even chiropractic work—can also help to prevent occupational injury.

I'm not one prone to Schadenfreude, but when a 2012 study found that 46 percent of ophthalmologists had neck pain, 26 percent had back pain, and 17 percent had wrist or hand pain, I was relieved—not because others were suffering, but because I wasn't alone.[1] I started having back pain during my second year of residency doing strabismus surgery, of all things. Since then, keeping my neck, back, wrists and now shoulders pain-free has been an ongoing endeavor.

Ophthalmologists have a higher risk of occupational injury than other physicians. One early study found that ophthalmologists reporting neck symptoms tended to be younger and were more likely to be women, tended to be in practice for fewer years, and reported higher stress levels.[2] Interestingly, the authors found that musculoskeletal issues seemed to be independent of the number of patients or surgeries performed. However, other studies demonstrated that repetitive work injuries seemed to increase along with the workload.[3]

The main reasons for our work issues are poor posture, repetitive motions and the fact that we repeatedly maintain really awkward positions such as using the headlamp or hunching over the slit lamp.[4-6] In this article, I'll explain the causes of our problems with occupation-related injury, and then share a few solutions.

The problems

Our workflow isn't designed for the long-term health of our own bodies, as these four elements of our routine illustrate:

• ***Exam room setup.*** Our computers are set up against one wall with the patient's chair 90 degrees away (*Figure 1*). After I walk into the room, I stand in front of the patient and turn my head 90 degrees to look at the screen—clearly not a recipe for spinal happiness. Rather than

Bio

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DISCLOSURES: Dr. Garg has no relevant financial relationships to disclose.

sitting properly, I tend to crouch over and start typing while sitting awkwardly.

• ***The slit lamp.*** While the slit lamp is an amazing piece of design and engineering, it induces bad posture. Due to the fixed position of the oculars, many of us end up hunching forward. Holding the condensing lens with our arms outstretched puts stress on our shoulders and upper back, and grasping the lens causes wrist and hand problems. Additionally, the slit lamp tables are often unnecessarily large, forcing us to sit back farther from the slit lamp. Those of us with larger torsos and/or abdomens also have to sit farther back, additionally causing dorsiflexion of the neck.

• ***Indirect ophthalmoscopy.*** Here, we end up standing in awkward positions and twisting our neck from side to side, all of which sets us up for musculoskeletal issues in the future.

• ***The operating room.*** Mostly we use whatever chairs, OR tables and microscopes are available. I use a Machemer stool, which is really comfortable; however, the wide circular base sometimes hits the foot pedals, which I then have to push farther from me. The oculars may or may not tilt enough to enable us to sit upright. When I'm operating with our fellows, the poorly positioned assistant scope forces me to sit side-saddle because there isn't enough room for my legs under the table.

The solutions

There are a number of things we can do to help reduce injury. Here are some ideas:

• ***In the clinic.*** The examination stool can hit the footrest, which forces us to sit farther back, requiring us to lean forward to get to the oculars and then tilt back our heads in order to look straight on. Doing something as simple as lifting up the footrest allows me to slide my chair closer to the patient, enabling me to sit more upright (*Figure 2*).

• ***Slit lamp table.*** It's often positioned unnecessarily deep, forcing us to sit farther away from the patient, functionally creating a posture similar to what was happening when the footrest was down. Getting a narrower slit lamp table is possible, but often equipment manufacturers and suppliers aren't aware or aren't equipped to help us with this. Physicians that have done this usually hire outside contractors to make a new table. It doesn't take much time, and it's not expensive, but it does require effort to find someone to do the job.

Figure 1. The computer system is at a 90-degree angle to the patient, which requires quite a twist to see the patient. Sitting properly also reduces the need to hunch over. (*Photos by Alexa Bednar)*

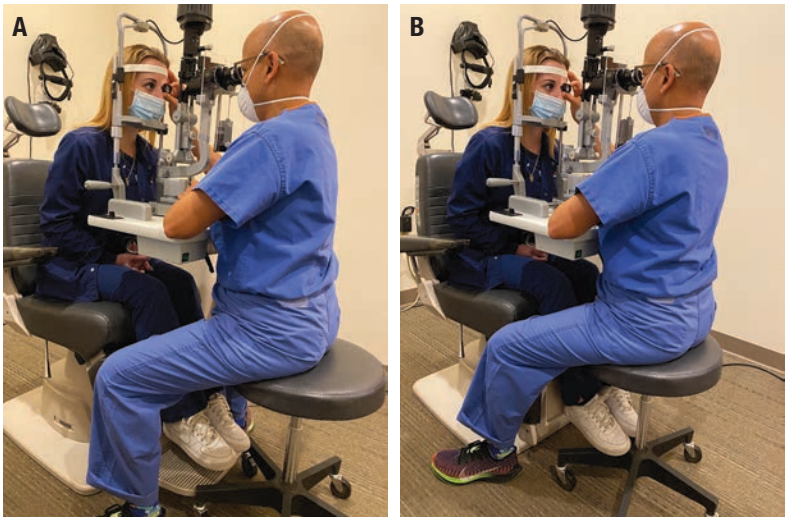

Figure 2. A) When the footrest is down, the rolling stool can move forward, causing you to lean forward and dorsiflex your neck. B) Lifting the footrest lets you position the stool closer to the patient so you can sit more upright.

Figure 3. What not to do: Tilting the oculars down requires you to look up, leading to neck dorsiflexion. Adjusting the oculars so you look straight ahead or down allows the neck to be in a more neutral position. (*Photo by Kathryn Lynn*)

In the OR, I first make the chair height comfortable for me. I put the foot pedals where I want them. Next, I bring the microscope into position and put the oculars at a comfortable angle. Only then do I adjust the bed so the eye is in focus.

• ***Condensing lens.*** Holding the condensing lens with your hand neutral is generally the best position; flexing or extending the wrists causes unnecessary strain. An elbow rest made of foam can also relieve some shoulder strain.

In the OR

I stress the importance of positioning to my fellows. Often I see the patient wheeled into the room, basically left where they are on the bed. The fellow drops the microscope in, sort of adjusts the chair, and then hunches over or stretches to reach the oculars. This might be acceptable for a few cases when you're 30, but it's definitely not a recipe for long-term well-being. A better approach is to remake the OR environment so it's centered around the surgeon. Here are some steps I take to accomplish that:

• ***Chair height and microscope positioning.*** Essentially, I first make the chair height comfortable for me. I put the foot pedals where I want them. Next, I bring the microscope into position and put the oculars at a comfortable angle, ideally looking straight ahead or slightly down (*Figure 3*). Only then do I adjust the bed so the eye is in focus. By doing this, I don't force my body to adapt to the machinery; instead, I adapt the machinery to my body.

• ***Patient positioning.*** I also ensure the patient is at the very top edge of the bed. A lot of times I see my fellows put the top of the patient's hair at the top of the bed, but if someone has a beehive that can still position their eye two feet away. Also, I'll see people level the top of the patient's head to the cushion, but the cushion itself is also halfway in the middle of the bed. I'm very particular about making sure the patient's head is at or slightly over the top of the metal portion of the stretcher. This enables me to put the patient's head essentially adjacent to my abdomen, allowing me to sit upright.

Some surgeons have suggested that a heads-up display may be more ergonomic, as it frees the surgeon from the confines of the microscope. I haven't found the current iterations of the heads-up display systems I've used to be advantageous in this regard.[7,8]

• ***Proper wrist rest use.*** When we routinely used 20-gauge vitrectomy or non-valved cannulas, there was a tremendous loss of fluid. Unless you wanted to have a wet leg, the trough needed to be supported by the wrist rest. With valved cannulas, there's little fluid loss during our cases, so this use of the wrist rest is less important.

Some surgeons use the wrist rest as a way to help stabilize their hands and take some of the load off their arms. However, most of my trainees use the wrist rest as a decoration. The problem with using a wrist rest unnecessarily is that it also separates you from the patient's head by 3 to 4 inches. Similar to what we were encoun-

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UPCOMING EVENTS

Ergonomics of the body and mind: Yoga and other remedies

We can do a number of things to keep our bodies in good shape. When I started developing back pain during residency, a neighbor suggested that I start doing yoga. Almost immediately my back pain went away. To this day, I consistently practice, otherwise the back pain returns.

Yoga has also helped increase my body and mind awareness. This helps me pay attention to my body alignment, and has helped me maintain a greater degree of awareness, not only of what I'm doing in the eye, but also of all that's happening in the OR as well.

I've occasionally been in circumstances where things were going in an unintended direction. I'm able to be aware of when my anxiety increases, and I have strategies to help quiet my mind and body to handle the situation in front of me.

There is a specific form of yoga called Iyengar Yoga. This is definitely not the Lululemon set who can put their big toe in their ear! An essential part of an Iyengar teacher's education is helping people maintain different postures as their body allows, using props when necessary so the student can get the benefit of a posture while reducing any risk of injury. The attention to form and process, I think, is well suited to the ophthalmology mindset.

Pilates can also be a great exercise. Much of what we do involves good upright posture which needs good core strength—Pilates' forte. Other forms of physical therapy, massage and chiropractic work can also be of benefit.

–S.G.

As a profession, we need to better engage with industry to improve the ergonomics of our work environment. Awareness and physical conditioning can only do so much.

tering with improper head positioning, the wrist rest forces you to sit back farther from the patient, requiring most of us to then tilt slightly forward, exacerbating neck or back pain.

• ***Positioning the arms.*** It's important to keep your arms hanging loosely at your side. I've seen people who operate with their arms out to the side and their elbows pointed to the corners of the room sort of like they're getting ready to do the chicken dance at a high school prom. The only other reason to do this is because your underarms are getting all sweaty. If that's the case, consider investing in a better deodorant.

Advocacy

As a profession, we need to better engage with industry to improve the ergonomics of our work environment. Awareness and physical conditioning can only do so much. A few years ago the American Academy of Ophthalmology had a task force on ergonomics. This group identified a number of strategies, including extended oculars, improved slit lamp ergonomics and ergonomically friendly computer workstation changes. Many of these changes aren't things that we can do by ourselves. We need to push our societies and equipment manufacturers to address this issue now so that we and our other colleagues can reap the benefits for years to come.

Recently Dr. Garg, along with Samuel Masket, MD, Alison Early, MD, and Luisa DiLorenzo, MD, hosted an American Academy of Ophthalmology webinar on ergonomics. It's available at https://aao-org.zoom.us/webinar/register/WN_M96tsbCiQL-qC3iKFX7Ipg

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EO: If you do it, you should bill it

Extended ophthalmoscopy is a charge retina specialists commonly miss. Here's how to bill for it.

By Ellen R. Adams, MBA

By now you should be comfortable with the new Evaluation and Management (E/M) coding rules. If you're using the E/M codes correctly, your revenue compared to previous years should be about level. (Of course, if it is level, that means your effective revenue has declined.)

A savvy retina specialist will perform, document and bill all services performed on a given date of service. For example, a commonly missed charge is extended ophthalmoscopy. As a vitreoretinal specialist, a part of your stock in trade is doing EO. Let's look at what you need to do and document in order to bill for this service that you perform regularly.

In previous versions of CPT, EO was billed as "initial" or "subsequent." Importantly, in January last year the CPT for EO was overhauled to allow charges for a macular/optic nerve exam or a peripheral retinal exam. The initial or subsequent definition was dropped entirely.

Macular exam

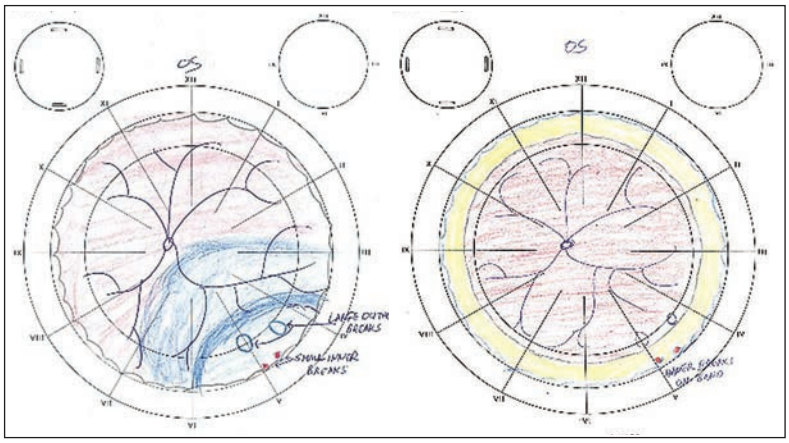
CPT defines the macular exam as: "Ophthalmoscopy, extended, with drawing of optic nerve or macula (e.g., for glaucoma, macular pathology, tumor) with interpretation and report, unilateral or bilateral." The CPT code is 92202. There's no defined limitation of services for this code.

However, payment is only appropriate if there's serious disease and a documented change in appearance to support the charge. Your documentation should, of course, include an exam note that supports the macular EO.

You must have a scaled, labeled, separate drawing above and beyond your usual macular documentation. Payers differ on the required size of the drawing and whether the drawing should be in color, so check your local payer policies to be sure you meet any specific size and color requirements. Those payers that have policies usually specify that drawings be 3 to 4 inches or larger; in any case, they must be large enough to show significant detail.

Peripheral retinal exam

The definition for the peripheral retinal exam is more specific: "Ophthalmoscopy, extended, with retinal drawing and *scleral depression* of peripheral retinal disease (e.g., for retinal tear, retinal detachment, retinal tumor) with interpretation and report, unilateral or bilateral" [emphasis



Scaled, labeled drawings such as these, depicting retinal detachment secondary to retinoschisis detachment in the left eye, are key components of the documentation for extended ophthalmoscopy. (*Courtesy William H. Ross, MD, FRCSC*)

Have a question for "Coding Commentary"? Tweet it to us at @RetSpecMag

Bio

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added]. The CPT code for this service is 92201. As with macular EO, there's no defined limitation, but again, payment is appropriate only if the disease has changed in appearance. The specifications are also more clearly defined:

- Retinal drawings must be maintained in the patient's record.
- Drawings should include sufficient detail, standard colors and appropriate labels.
- Individual drawings should be made for each eye.
- The drawing must be separate and distinct from the comprehensive eye exam.
- An assessment of the change from prior exams when performing follow-up services is required.

Payer requirements vary, and they may also include scaling the drawing to depict relative size, coloring it using classical representations (that is, red for hemorrhage, blue for detachment, etc.), and notating that the eye was dilated and the dilating agent used. Again, review your Medicare carrier policies for specific requirements.

Charging for extended ophthalmoscopy is appropriate when you're performing the test to document serious retinal pathology. You shouldn't bill either EO charge when the exam is normal.

Documentation requirements

For either code, the documentation must be legible. It's important that you indicate the type of exam performed, such as whether it was done with a 90-D lens with the slit lamp (for 92202), or with a 20-D lens with the patient supine and that scleral depression was performed (for 92201). Also, the documentation should note whether any anesthesia was needed and, although rare, if any complications were encountered or if the test was uncomplicated.

An important point to reiterate is that this charge is appropriate when you're performing the test to document serious retinal pathology. You shouldn't bill either EO charge when the exam is normal.

Many electronic medical records systems allow you to "carry forward" a macula or peripheral drawing. However, you must avoid duplicative documentation, and only bill for EO when you've created a new and clearly unique drawing.

The 2021 national Medicare payment rate for macular EO is $25.12; the peripheral EO rate is $16.05. Commercial payments may be higher. And before you discount the value of billing a properly documented EO, consider how often you currently perform this service without billing for your time and expertise.

A word about bundling EO

In a previous article we discussed national correct coding initiative (NCCI) edits, colloquially called "bundles," which impact ophthalmology services. These bundles will result in claim denial when disallowed services are billed on the same date of service.

Like many ophthalmic tests, EO has edits that you should keep in mind. First and foremost, EO is bundled with fundus photography (92250). However, EO isn't bundled with fluorescein angiography or scanning computerized ophthalmic diagnostic imaging (SCODI), but carriers specify that EO performed on the same date of service as FA or SCODI should provide information that the other tests didn't.

EO is also bundled with all retinal surgeries. However, some insurance carriers will deny payment for EO during the postoperative period of a retinal procedure. Again, check your local Medicare policies to avoid billing statutorily denied charges.

EO is a valuable and often-performed procedure in the retinal clinic. When it's warranted and you do it, you should bill for it.

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1. 92201, 92202 Extended Ophthalmoscopy. CPT Professional 2020. 1st ed. Chicago, IL: American Medical Association; 2019.
2. Centers for Medicare and Medicaid Services. Medicare Physician Fee Schedule Look Up Tool. Updated July 1, 2021. Available at: https://www.cms.gov/medicare/physician-fee-schedule/search?Y=0&T=4&HT=1&CT=0&H1=92201&H2=92202&M=5

A potential stem-cell solution for GA

Trial shows safety of a biosynthetic patch inserted in a subretinal bleb in an outpatient procedure.

Clinical programs for the treatment of geographic atrophy have taken on an almost Holy Grail-type mystique. At least 10 candidates targeting different pathways to treat the end-stage effects of dry age-related macular degeneration were in human trials at the start of the year.

A San Francisco Bay area company is pursuing a different approach for GA. At the International Society of Stem Cell Research 2021 meeting in June, Jane Lebkowski, PhD, president of Regenerative Patch Technologies, reported results of the Phase I/IIa trial of its CPCB-RPE1 implant (NCT01590692) for treatment of severe vision loss from GA.

CPCB-RPE1 is a bioengineered implant consisting of stem cell-derived, mature, polarized retinal pigment epithelial cells on what the company describes as an "ultrathin" synthetic parylene membrane. It's placed in a subretinal bleb overlying the area of GA to replace damaged RPE and Bruch's membrane.

Here, Amir H. Kashani, MD, PhD, associate professor of ophthalmology at Wilmer Eye Institute, Johns Hopkins University in Baltimore, answers questions about the technology and the clinical investigation. Dr. Kashani is the lead trial investigator for the Phase I/IIa study and was formerly on faculty at the University of Southern California, which is one of three entities—California Institute of Technology and University of California Santa Barbara are the others—that have licensed the technology to RPT. He has no financial interest in the company or technology, but USC has received grant support from RPT for conducting the clinical trial.

Q Please describe the CPCB-RPE1 implant in your own words.

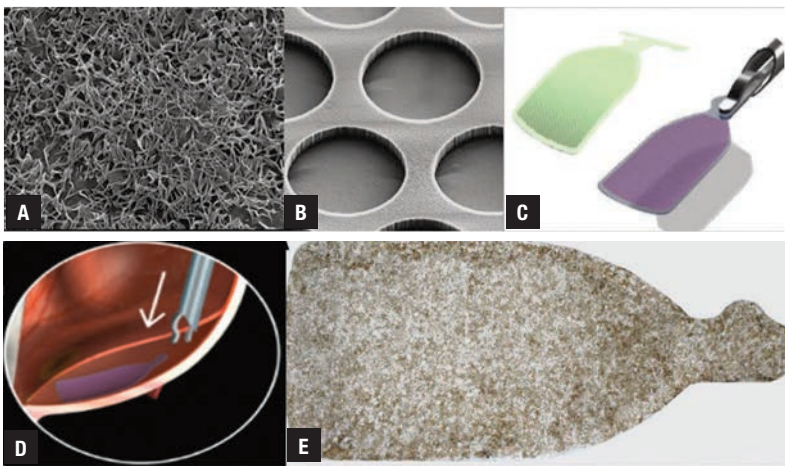
A This biosynthetic implant consists of an RPE monolayer derived from stem cells and adherent to a synthetic parylene membrane that mimics the diffusion properties of Bruch's membrane. The implant is approximately 3.5-x-6.25-mm in area and 6 µm thick with ultrathin regions less than 1 µm thick. It's designed to be delivered into the subretinal space and within the area of GA in an outpatient procedure.

Q Where did the idea come from to use a stem-cell implant to treat GA?

A Over the past several decades a number of clinical trials attempted either macular translocation surgery or autologous RPE transplantation in patients with both wet and dry AMD. And the question was, knowing that GA involves an area of the retina where RPE cells are dying or dead, would it help people see if we put fresh or new RPE cells in that area?

In the early days of stem-cell research, we didn't have the technology to derive RPE cells from stem cells, so surgeons had to surgically harvest RPE cells from another part of the patient's eye, or potentially from other sources, such as animals or human fetuses.

By Richard Mark Kirkner, Editor



Five views of the CPCB-RPE1 implant: A) mature retinal pigment epithelium cells on the implant; B) the parylene membranes used as a scaffold to support the RPE cells; C) a rendering of the delivery tool along with the implant showing how the tools grasp and compact the implant for delivery; D) a rendering of implant delivery into the subretinal space of the eye; E) a magnified view of the actual implant. (*Courtesy Regenerative Patch Technologies*)

However, those sources came with practical limitations as well as ethical issues that prevented widespread availability. Most importantly, surgically harvesting autologous RPE was a traumatic process that often caused proliferative vitreoretinopathy.

Nevertheless, autologous RPE transplantation was done in several studies. Even though these surgeries were complicated and difficult, a handful of patients showed promising visual acuity improvements. They provided a proof-of-concept that RPE replacement can work.

Q How does the parylene membrane help to integrate with the host tissue?

A Parylene is a bioinert substance with a US Pharmacopeia Class VI rating for medical grade safety. It has been used for decades in many human device implants because it doesn't elicit an inflammatory response, and it doesn't degrade or dissolve. There's extensive knowledge about its safety and biocompatibility.

Engineers at USC and Caltech have been able to machine parylene down so that the CPCB-RPE1 implant has areas of parylene that are less than 1 µm thick. *In-vitro* studies have shown that a number of macromolecules that would theoretically diffuse through Bruch's membrane can also diffuse through the ultrathin regions of the parylene membrane.

Parylene has been used for decades in many human device implants because it doesn't elicit an inflammatory response, and it doesn't degrade or dissolve. There's extensive knowledge about its safety and biocompatibility.

Q What were the results of the Phase I/IIa trial?

A Fifteen patients were implanted with the CPCB-RPE1 during outpatient surgery. Preliminary results of the first four patients to receive the implant were reported in 2018[1] and detailed methods of the surgery were described in a subsequent paper in 2020.[2]

These studies demonstrated a few important points. First, it was feasible to do the surgery with commercially available surgical instrumentation. Second, the success of the surgical procedure in targeting the area of GA was very high. Third, the implant appeared to retain viable RPE throughout the post-implantation period without clinical evidence of immune rejection.

Most importantly our recent results demonstrated that the implant and surgery are safe and well tolerated out to one year.[3] We also observed that more eyes that received the implant gained vision while more non-implanted contralateral eyes tended to lose vision. This potential efficacy is promising but only preliminary and has to be verified in a subsequent clinical trial.

Q Can you briefly describe the surgery itself?

A The surgery is an outpatient procedure performed using commercially available vitrectomy equipment, including core vitrectomy, peripheral vitreous shaving and raising of a subretinal bleb in the peri-GA region.[2] The delivery device is inserted through pars plana vitrectomy incisions and the implant is injected into the subretinal space through a retinotomy that's about 1 mm wide.

After the implant is delivered into the subretinal space, the retina is flattened with perfluorocarbon, air-fluid exchange and intraocular tamponade (silicone oil or gas).[2] We used silicone oil for this pilot study because we were worried the implant may migrate, but that wasn't a problem at all. We're planning on using air or gas tamponade in our next trial which will also shorten the duration of surgery even more.

We used commercially available 23-gauge vitrectomy instrumentation for the entire procedure, except for the implant insertion which was done with the custom injector. RS

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1. Kashani AH, Lebkowski JS, Rahhal FM, et al. A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration. Sci Transl Med. 2018;10:eaao4097.
2. Kashani AH, Uang J, Mert M, et al. Surgical method for implantation of a biosynthetic retinal pigment epithelium monolayer for geographic atrophy: Experience from a Phase I/IIa study. Ophthalmol Retina. 2020;4:264-273.
3. Kashani AH, Lebkowski JS, Rahhal FM, et al. One year follow-up in a Phase 1/2a clinical trial of an allogeneic RPE cell bioengineered implant for advanced dry age-related macular degeneration. Trans Vis Sci Tech. (In press).

LUCENTIS®
RANIBIZUMAB INJECTION

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

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

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

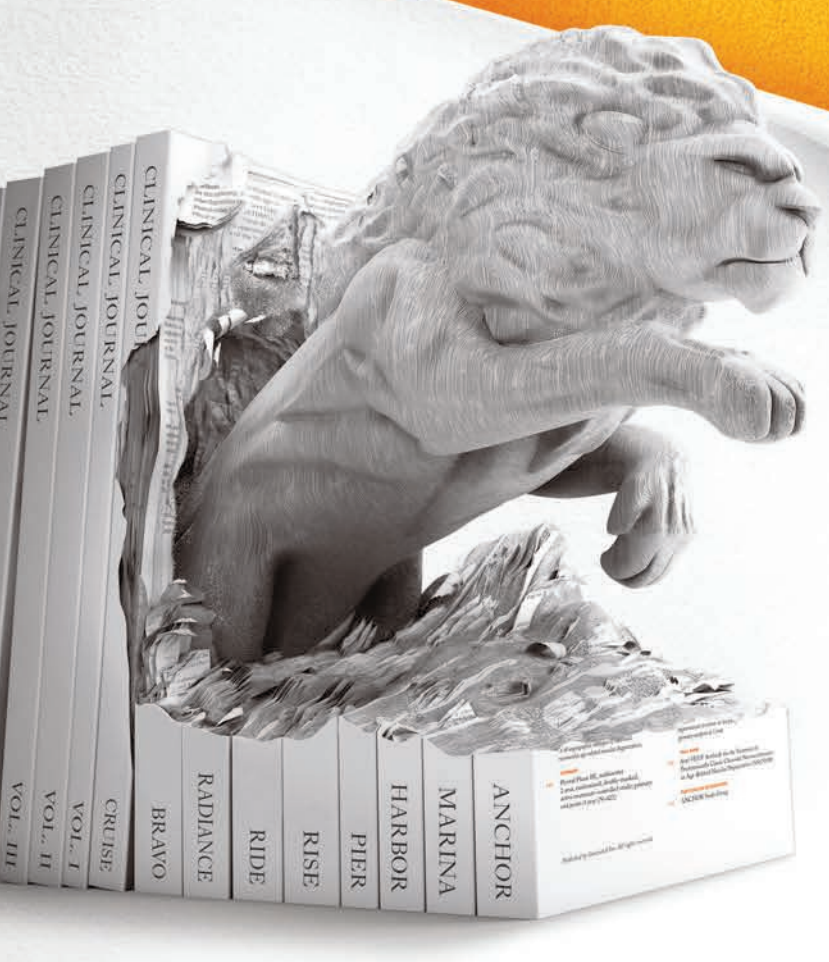
10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

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

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

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

LUCENTIS®
RANIBIZUMAB INJECTION



STRENGTH IN VISION

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

INDICATIONS

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

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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