A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

VOL. 7, NO. 2 • MARCH/APRIL 2021

Retina Rounds: A curious case of retinal artery microaneurysm Page 16

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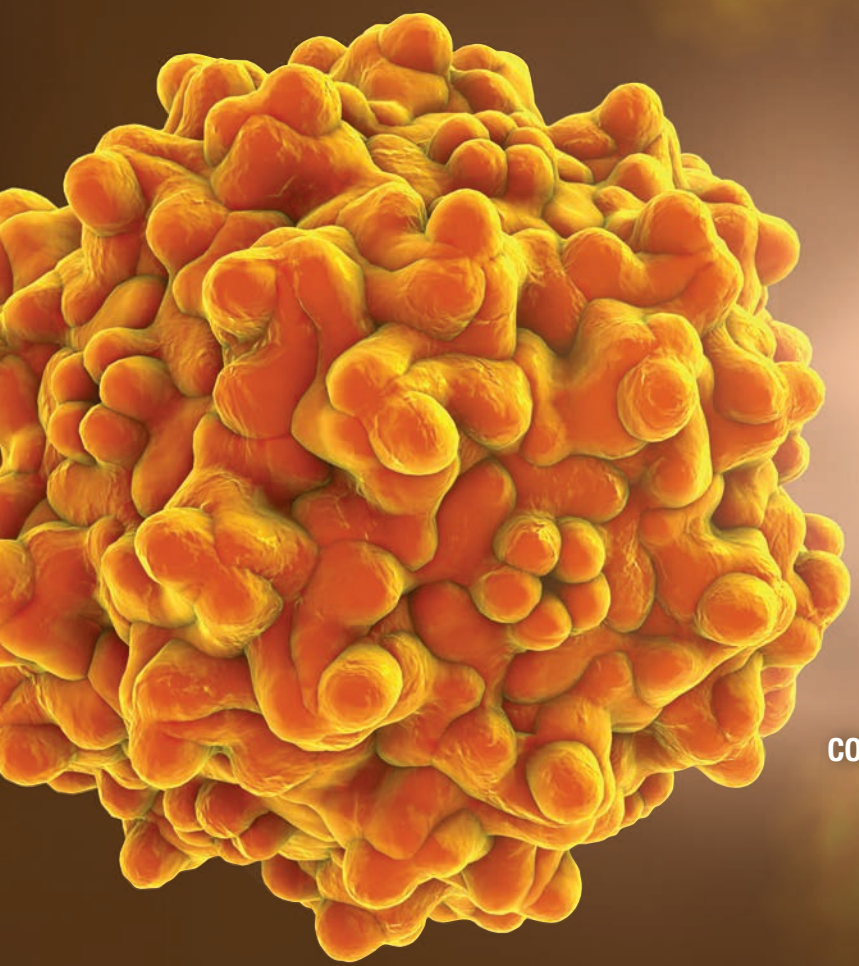

OCULAR GENE THERAPY: THE NEXT GENERATION

Emerging viral and synthetic vectors and new delivery systems are broadening treatments. *Page 22*

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

Discover continuous calm in uveitis

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

- **Proven to reduce uveitis recurrence at 6 and 12 months[1]***
  [At 6 months–18% for YUTIQ and 79% for sham for study 1 and 22% for YUTIQ and 54% for sham for study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for study 1 and 33% for YUTIQ and 60% for sham for study 2.]
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*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, phase 3 studies in adult patients (N=282) with noninfectious 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 noninfectious uveitis, or the use of prohibited medications.[1,3]

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic noninfectious 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.

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 U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018. **2.** EyePoint Pharmaceuticals Receives FDA Approval of YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg. Global Newswire. https://www.globenewswire.com/news-release/2018/10/15/1621023/0/en/EyePoint-Pharmaceuticals-Receives-FDA-Approval-of-YUTIQ-fluocinolone-acetonide-intravitreal-implant-0-18-mg.html. Accessed February 7, 2020. **3.** Data on file.

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02/2021
US-YUT-2100009

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

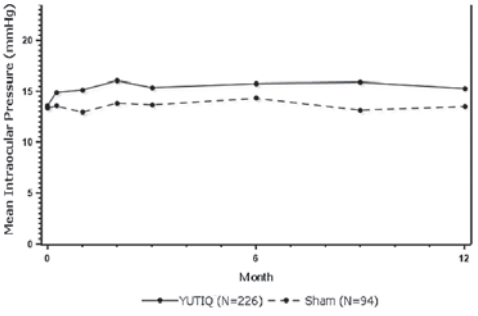
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

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EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
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19 Campus Blvd., Suite 101
Newtown Square, PA 19073
Telephone (610) 492-1000
Fax (610) 492-1039

Editorial inquiries (610) 492-1000
Advertising inquiries (610) 492-1011
E-mail retinaspecialist@jobson.com

EDITORIAL

By Charles C. Wykoff, MD, PhD

Asymptomatic patients

It's hard to make an asymptomatic patient better.

When patients present with a macula-off retinal detachment, an acute central retinal vein occlusion or a central sub-retinal hemorrhage due to neovascular age-related macular degeneration, the need for intervention is obvious from both the patient and physician perspectives.

However, many pathologies in our realm involve patients who aren't acutely symptomatic. These clinical scenarios demand a more nuanced discussion with patients about management options, including observation, and the specific risks and benefits of each.

The most obvious of these we've discussed for the last many years involves patients with severe non-proliferative diabetic retinopathy without diabetic macular edema. Accumulating prospective data indicate that earlier initiation with anti-VEGF pharmacotherapy yields tangible benefit, on average, for this population. Nevertheless, there are numerous arguments supported with data on both sides of this theoretical debate, and the ultimate decision to initiate therapy must continue to be an individualized approach, highly dependent on the specific clinical circumstances of each patient.

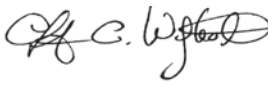
A more thorough understanding of which patients may benefit the most from earlier interventions may assist our decision-making, and artificial intelligence systems, as Dr. Grayson Armstrong discusses on page 30, continue to hold great promise for improved prognostication.

Retinal breaks are another clinical scenario we all encounter regularly. Drs. Jonathan Russel, Bill Smiddy and Harry Flynn beautifully summarize excellent clinical pearls related to their management on page 34. While we can all agree that acute, symptomatic retinal tears should be treated, many breaks and other retinal pathologies such as lattice degeneration can fall into the gray zone of management.

A few years ago, my parents came to visit and I decided to examine my Dad's retinas. He had a few drusen consistent with his demographic and some mild vascular changes consistent with his age. On peripheral exam of his left eye, I found a superior, horseshoe retinal tear at the vitreous base with obvious residual vitreous traction, a small cuff of subretinal fluid and no pigmentation. He was asymptomatic. What would you do?

I laser demarcated the break and referred him to a friend of mine for follow-up in California. To this day, my Dad jokes about how I "blinded" him with my laser despite him being asymptomatic before and after the laser. I then remind him that I may have saved him from needing a vitrectomy. He then typically wins the debate by saying at least he could have gotten rid of his floaters.

Even though Benjamin Franklin was probably right when he said an ounce of prevention is worth a pound of cure, context is everything. Be careful with asymptomatic patients!



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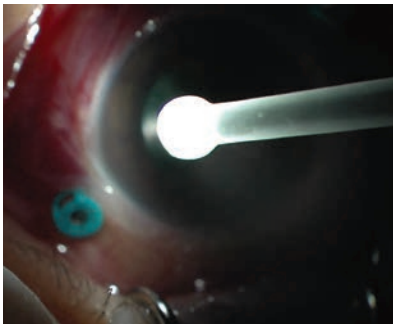

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COVID-19 dealt retina surgical procedures a big blow; effects may linger for a while

An analysis of billing data from 17 large retina centers across the United States has documented a sharp decline in urgent or emergent vitreoretinal surgical procedures during what we now know are the early days of the COVID-19 pandemic.[1] Even as vaccines roll out and the country moves toward herd immunity, the effects of the pandemic on retina practices may linger for the foreseeable future, the lead author of the study says.

"I think the study raises important questions; the return to 'normal' is probably going to take longer than any of us anticipated," lead author Mark P. Breazzano, MD, says in an exclusive interview with *Retina Specialist Magazine*. Dr. Breazzano is an assistant professor at Wilmer Eye Institute of Johns Hopkins University in Baltimore.

Quantifying sharp declines

The study collected billing data on 526,536 procedures from 17 academic and private retina practices across the United States and compared weekly surgical and procedural volumes for March 16 to May 31, 2020—the period when stay-at-home orders were imposed in the states represented in the study—with the corresponding period from 2019.

Mark B. Breazzano, MD

The study reported these average maximal weekly declines at each institution for the following procedures:

- ***Intravitreal injections*** (IVI), a 38.6-percent decrease from April 6 to 12, from an average of 437.84 per institution in the corresponding week in 2019 to 273.82 (p=0.002).
- ***Laser/cryotherapy***, a 79.6-percent decrease for the same week, from 6.57 procedures per institution to 1.52 (p<0.001).
- ***Retinal detachment repairs***, a 59.4-percent decrease April 13 to 19, from 3.45 per institution to 1.55 (p<0.001).
- ***Other vitrectomies***, an 84.3-percent decrease for April 6 to 12, from 2.98 procedures on average to 0.75 (p<0.001).

Dr. Breazzano notes that the declines were across the board and didn't deviate regardless of region or practice setting (academic or private).

Potential role of AAO guidance

As stay-at-home orders were sequentially issued by each state, the American Academy of Ophthalmology released a list of urgent and emergent surgical procedures[2] to guide ophthalmologists on prioritizing care during the pandemic. "I believe this guidance was helpful for us in managing these patients because there was considerable uncertainty during this period. The objective was to simultaneously preserve vision and optimize safety from COVID-19 infection," Dr. Breazzano says of the AAO list.

"I'm not sure what would've happened without the recommendation," he adds. "It is fortunate that we had this guidance up front, and I imagine a more substantial decline may have followed without AAO support."

Sorting out reasons for declines

Dr. Breazzano notes that IVI declined less than other procedures. Besides the reluctance of patients to come into clinics during the pandemic for fear of COVID-19 infection, another potential factor may have been the stay-at-home orders themselves limiting peoples' normal movements and activities, thus reducing cases of

IN BRIEF

The Food and Drug Administration has approved the **Argus 2s Retinal Prosthesis System**, a redesigned combination glasses-and-video processing unit initially made for use in combination with the Argus II systems implanted for retinitis pigmentosa. **Second Sight Medical Products** says it will adapt the Argus 2s to be the external system for the **Orion Visual Cortical Prosthesis System** currently under development.

Graybug Vision has reported preliminary topline data from the 12-month treatment phase of the Phase IIb ALTISSIMO trial of **GB-102**, an intravitreal formulation of sunitinib malate, for wet age-related macular degeneration. For patients in the 1-mg arm, the average time to the first rescue treatment was five months. Overall, the 1-mg dose was well-tolerated with no drug-related serious adverse events. Twenty-two patients have completed at least two months of this six-month extension period without the need for further treatment.

A biosimilar of aflibercept recently completed a Phase I trial in South Korea. **Alteogen** reports that **ALT-L9** met safety and efficacy endpoints comparable to those of aflibercept. The company says it intends to pursue a Phase III trial.

vitreoretinal traction and the ensuing retinal tears and detachments.

However, it's unclear whether these patients may present later with late-stage complications from waiting with a retinal detachment, including additional scar tissue from proliferative vitreoretinopathy. Reduced cataract surgery and other elective procedure volumes may have also led to fewer related vitreoretinal complications.

Another explanation for the disparity between IVI and other procedures is the regularity with which IVI patients return to the clinic. They're connected to the health-care system, Dr. Breazzano says. "But let's say we have somebody arriving with a retinal detachment referred by another doctor; it may be challenging for them to enter that system," he says. "New precautionary measures implemented by health systems as a reaction to minimize COVID-19 infection may have also impeded these urgent referrals."

That may also be a consequence of clinic staff working remotely. "Some of this remote and virtual work might add difficulty in identifying and integrating these patients into the system, and therefore managing the high-acuity condition," Dr. Breazzano says.

Lessons going forward

As retina practices emerge from the pandemic, there are lessons that may endure, Dr. Breazzano says.

"I think we've learned that certain, simple precautions are quite effective—such as slit lamp shields, wearing masks, and minimizing crowding in the waiting and office spaces with family members and caregivers of patients—in helping reduce the transmission of pathogens," he says. He notes that cases of the common cold and seasonal flu declined markedly with mask-wearing and other pandemic-related precautions.

Even with herd immunity on the horizon, ophthalmologists must continue to be vigilant. "We know that ophthalmology has a uniquely higher increased infection risk compared to other physician specialists, and it's likely bidirectional for our patients, too,"[3] Dr. Breazzano says. "We could potentially give it to them in the same way they could give it to us."

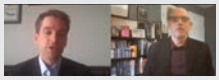
Dr. Breazzano adds, "Ophthalmologists are at higher risk. We know this given our proximity to the face, and the secretions around the face that we're constantly exposed to, as supported by our data from New York City resident physicians infected early in the pandemic. The first indication of a strong connection between COVID-19 and our specialty was evident by the Chinese ophthalmologist Li Wenliang, the physician who initially sounded alarm bells and ultimately died with COVID-19.

"It's going to be something that I think that we all as ophthalmologists and retina specialists will carry with us," he adds. "Given the increased risk for our patients and staff, anything that can be gleaned, including these simple measures, will be important moving forward." RS

—Richard Mark Kirkner

Watch our interview

Mark Breazzano, MD, explores the study findings in detail in this interview with Richard Kirkner, editor of *Retina Specialist* at http://bit.ly/RetSpecMag-202107.



REFERENCES

1. Breazzano MP, Nair AA, Arevalo JF, et al. Frequency of urgent or emergent vitreoretinal surgical procedures in the United States during the COVID-19 pandemic. JAMA Ophthalmol. Published online March 4, 2021. doi:10.1001/jamaophthalmol.2021.0036
2. American Academy of Ophthalmology (2020). List of urgent and emergent ophthalmic procedures. Posted March 27, 2020. https://www.aao.org/headline/list-of-urgent-emergent-ophthalmic-procedures. Accessed March 12, 2021.
3. Breazzano MP, Shen J, Abdelhakim AH, et al; New York City Residency Program Directors COVID-19 Research Group. New York City COVID-19 resident physician exposure during exponential phase of pandemic. J Clin Invest. 2020;130: 4726-4733.

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BUSINESS OFFICES
19 CAMPUS BOULEVARD, SUITE 101
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

EXECUTIVE DIRECTOR
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER
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CIRCULATION CUSTOMER SERVICE
PHONE: (877) 529-1746 (U.S)
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SENIOR CIRCULATION MANAGER
JARED SONNERS
(973) 206-8091 jsonners@mdedge.com

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS
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SIGNIFICANT REDUCTION IN DR SEVERITY IN PANORAMA[1,2]

PANORAMA is the first phase 3 anti-VEGF trial specifically designed to study patients with moderately severe to severe NPDR without DME.

PANORAMA study design: Multicenter, double-masked, controlled clinical study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without CI-DME (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1 of 2 EYLEA dosing regimens or sham. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). Between week 52 and week 96, patients randomized to one of the EYLEA arms received a different dosing regimen.[2]

IMPORTANT SAFETY INFORMATION AND INDICATIONS

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

MORE PATIENTS ACHIEVED A ≥2-STEP IMPROVEMENT IN ETDRS-DRSS WITH EYLEA VS SHAM[1]

Proportion of Patients Achieving a ≥2-Step Improvement in ETDRS-DRSS* Score From Baseline[1,2,†]

Primary Endpoint			Exploratory Endpoint‡
Week 24	Week 52		Week 100
EYLEA Q8 and Q16 (n=269)	EYLEA Q8 (n=134)	EYLEA Q16 (n=135)	EYLEA Q16 (n=135)
58%	**80%**	**65%**	**62%**
vs 6% in the sham group (n=133)	vs 15% in the sham group (n=133)	vs 15% in the sham group (n=133)	vs 13% in the sham group (n=133)

P<0.01 vs sham at Week 24 and Week 52. Nominal *P*<0.01 vs sham at Week 100.

*Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale (ETDRS-DRSS): an established grading scale for measuring the severity of DR.

†Full analysis set.

‡The results of these exploratory endpoints require cautious interpretation, as a multiplicity adjustment has not been applied. Results are descriptive only.

anti-VEGF = anti–vascular endothelial growth factor; CI-DME = central-involved DME; DME = Diabetic Macular Edema; DR = Diabetic Retinopathy; DRSS = Diabetic Retinopathy Severity Scale; NPDR = nonproliferative diabetic retinopathy; Q8 = every 8 weeks; Q16 = every 16 weeks.

SEE MORE DATA TODAY AT HCP.EYLEA.US

WARNINGS AND PRECAUTIONS (cont'd)

- 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.

ADVERSE REACTIONS

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

INDICATIONS

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

References: 1. Wykoff CC. A phase 3, double-masked, randomized study of the efficacy and safety of aflibercept in patients with moderately severe to severe NPDR: week 100 results. Data presented at: Angiogenesis, Exudation, and Degeneration Annual Meeting; February 8, 2020; Miami, FL. **2.** EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019.

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

10/2020
EYL20.09.0078

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.

REGENERON

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

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

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

EYL.20.09.0052

Six frugal faves for retinal surgery

A sample of simple, safe and cost-saving ideas for common procedures and imaging techniques with accompanying videos.

By Pieter J.S. Van der Merwe, MBChB, Tina Felfeli, MD, James Rice, MBBCh, MPH, Jonel Steffen, MBChB, MMed, and Efrem D. Mandelcorn, MD, FRCSC

Pieter J.S. Van der Merwe, MBChB, MSc

Tina Felfeli, MD

James Rice, MBBCh, MPH

Jonel Steffen, MBChB, MMed,

Efrem D. Mandelcorn, MD, FRCSC

North of the border, we often have no choice but to be frugal when it comes to managing health-care costs. Here, we would like to share six of our favorite simple, safe and cost-saving ideas for common retina procedures and imaging techniques along with accompanying videos. The videos are available at www.retina-specialist.com.

1 Scleral depression with a naked light pipe

The ability to visualize and work in the region of the vitreous base is an integral step of many vitreoretinal procedures. We typically do this by either depressing the sclera under chandelier illumination or having a surgical assistant perform the scleral depression.[1]

Recently, the use of lighted scleral depressors has become more commonplace. Many companies have produced guards that are placed over the light pipe, giving it two properties that facilitate scleral depression. While using a smooth sleeve over the light pipe reportedly minimizes conjunctival trauma, we've found this step to be unnecessary and prohibitive from a cost-of-access perspective.

We reported on the use of a naked light pipe for transscleral depression,[2] in which the shaft of an unguarded light pipe is placed parallel to the scleral surface until the end of the light pipe is over the area of interest (*Figure 1*). The light pipe shaft is then turned more perpendicular and depressed until the peripheral retina comes into view.

Subtle adjustment of the orientation of the light source may then highlight the anterior vitreous or retinal plane. This technique allows the surgeon to operate independently with maximum control.

We find this technique particularly useful for removing residual inferior vitreous hemorrhage or small residual particles of dislocated cataract that can be caught in the vitreous base. They're are very nicely visualized with transscleral illumination.

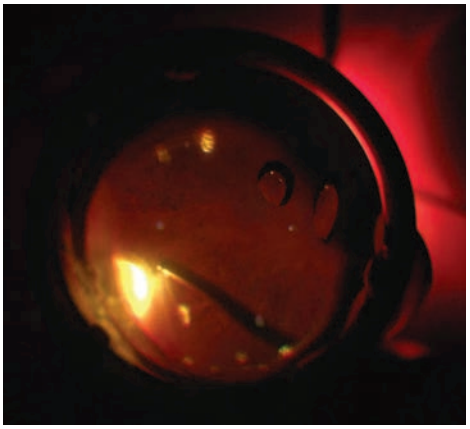

Figure 1. In scleral depression using a naked light pipe, the transilluminated scleral depressor provides enough internal light for safe vitrectomy and vitreous base shaving.

Watch the video at http://bit.ly/RetSpecMag-202101

2 Laser-light-assisted retinal membrane delamination

Retinal membrane delamination is the process of separating adhesions between membranes and the retina.

In our experience, the lighted curved laser probe has two properties that make it ideal for membrane delamination (*Figure 2, page 12*). First, its curvature, similar to the viscodissection cannula, as Jorge Fortun, MD, and Baker Hubbard 3rd, MD, reported,[3] allows the orientation of the probe to be parallel with the retinal surface.

This results in less traumatic blunt dissection and when pulling on membranes with forceps. Secondly, the light source allows for direct visualization of the membrane and retinal interface and may allow the surgeon to perform bimanual mem-

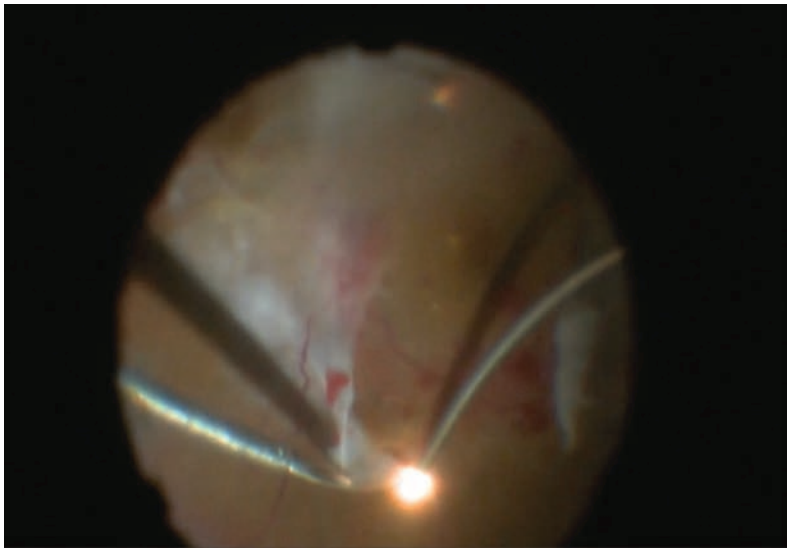

Figure 2. In laser-light-assisted retinal membrane delamination, the blunt curved end makes a perfect fit along the retinal surface and provides good visibility of the tissue plane.

brane manipulation without a chandelier.

Despite the usefulness of the lighted curved laser probe, it's important to note that when working so close to the retinal surface the lighting will be very intense in the immediate area, while visualization and illumination of the adjacent structures may be less clear. Be cautious when using the probe to perform blunt dissection to membranes very tightly attached to the retinal surface; this can lead to iatrogenic tears.[4]

The fact that the illuminated laser probe is often opened and paid for anyway in diabetic vitrectomy cases for the endoretinal laser portion of the surgery is another reason why it's one of our frugal faves.

Watch the video at
http://bit.ly/RetSpecMag-202102

3 A simple, passive backflush cutter

Draining subretinal or vitreous fluid can be achieved using both active and passive extrusion. Active extrusion could be done with the vitreous cutter or a backflush cannula, but passive extrusion was only for the backflush cannula—until now.

By simply opening the connection for the standard vitreous cutter you can create a passive extruding instrument that can help remove small amounts of residual fluid from the posterior pole or the edge of a retinal break in the final stages of the fluid-air exchange (*Figure 3*).

Watch the video at
http://bit.ly/RetSpecMag-202103

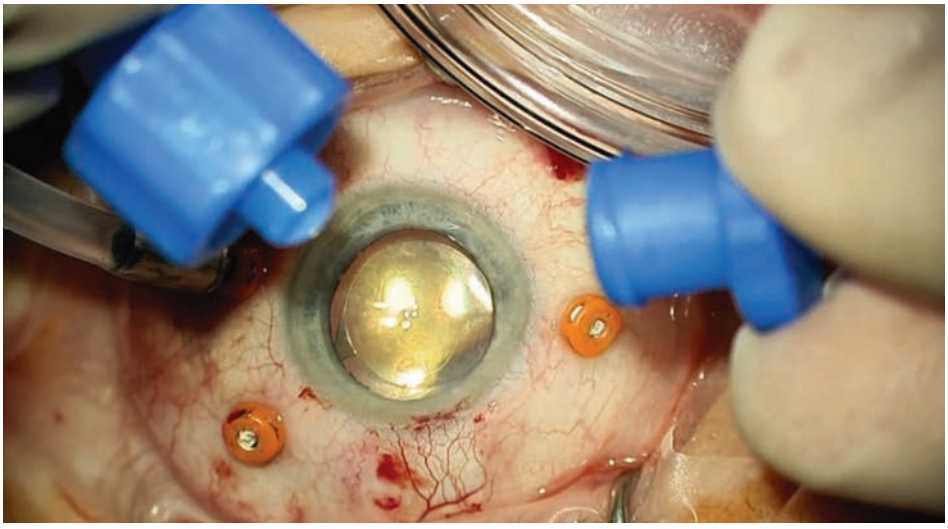

Figure 3. In the final stages of the fluid-air exchange, opening the connection for the standard vitreous cutter can create a passive extruding instrument to help remove residual fluid from the posterior pole or the retinal break edge.

Bios

Dr. Van der Merwe is a vitreoretinal surgery fellow at the University of Toronto.

Dr. Felfeli is an ophthalmology resident at the University of Toronto.

Drs. Rice and Steffen are consultant ophthalmologists at the University of Cape Town, South Africa.

Dr. Mandelcorn is an associate professor of ophthalmology at the University of Toronto.

DISCLOSURES: The authors have no relevant financial relationships to disclose.

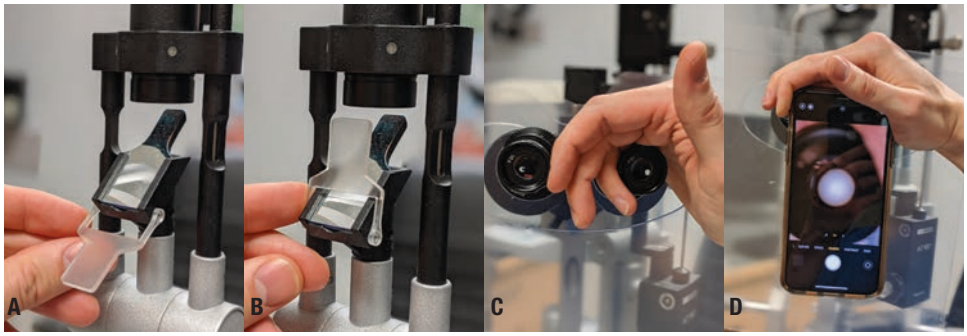

Figure 4. If your slit lamp has an integrated diffuser (A, B), you won't need to purchase an additional light source. Support your hand over the top of the oculars (C) and then grip the phone between your index finger and palm (D).

4 Slit-lamp smartphone photography

Several approaches to smartphone anterior segment photography that involve purchasing an adapter to attach to the slit-lamp have been described in the literature.[5] Given the frequent updates in sizes and shapes of smartphones, here we describe our step-wise approach for capturing high-quality images without the need for an adapter:

- ***Illumination.*** This should be diffuse, using either the slit-lamp or an indirect, diffuse light coming from the side. Check to see if your slit lamp has an integrated diffuser. If so, you won't need to purchase an additional light (*Figures 4A, B*).
- ***Camera settings.*** Have the flash turned off.
- ***Focus.*** Bring the slit-lamp into focus on the anterior segment as you usually do.
- ***Stabilize the camera.*** Instead of using a fancy smartphone-holding device, support your hand over the top of the oculars and then grip the phone between your index finger and palm (*Figures 4C, D*). This is the key.
- ***Focus and center the image.*** Move the phone closer or farther away from the slit lamp to find the appropriate focal distance for your phone. The appropriate focal distance is found when the circular image on your screen is entirely filled and in focus. Remember to focus the slit lamp before you focus the image on your phone. Move the phone up and down, left and right, and rotate it on the long and short axes to center the image on your screen.
- ***Take the picture.*** With your free hand, tap the screen to take the picture.

Watch the video at
http://bit.ly/RetSpecMag-202104

5 Cheap, assistant-controlled directional chandelier

Chandelier endoillumination has become common everyday practice for most

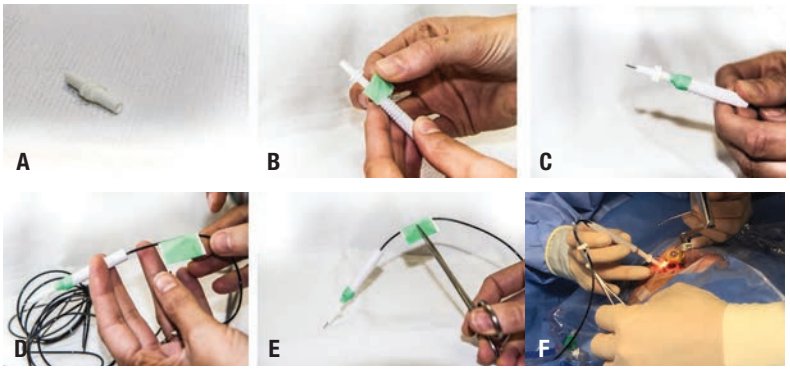

Figure 5. The male Luer connector (A) is attached to the light pipe label/adhesive dressing (B) to create a secure connection (C). To create the handle for the chandelier, fold the label/adhesive dressing on itself and around the optical fiber (D). This allows grasping of the chandelier (E) without crimping the optical fiber, which would damage it. The completed chandelier (F) can be held by the assistant without disrupting the surgeon's hands.

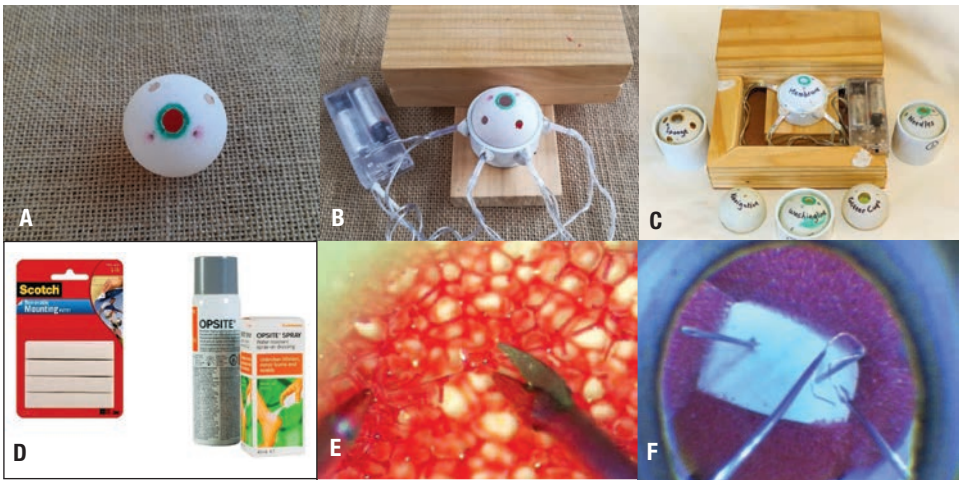

Figure 6. The low-cost retinal simulator consists of (A) the training "eye," (B) the completed simulator model without hardboard base and (C) with the hardboard base and examples of training eyes. The tools used in construction of training eyes (D) include reuseable adhesive putty (Scotch mounting putty) and spray-on membrane dressing (Op Site spray) to create membranes for dissection. Exercise tasks include (E) bimanual sponge dissection and (F) bimanual threading of an electrical wire loop through the eye of a needle.

This technique has several advantages. It allows for bimanual dissection. It provides bright, directional light. It's voice-controlled (grunt in the general direction of the fellow). It's reversible.

vitreoretinal surgeons, but these devices are costly and can't be controlled to minimize glare and direct the light where it's needed. Our solution for this is the "assistant-controlled directional chandelier." Here's what you'll need:

- a light pipe, standard on all PPV sets;
- male Luer connector (cheap or standard on most cataract PPV trays);
- Op Site/adhesive dressing/label to fixate tubing to the operative field;
- a snap, also standard on the PPV tray; and
- an assistant sitting to your right (usually with an excited and generally confused facial expression; standard at most training hospitals).

Stick the Luer connector to the light pipe with adhesive dressing, leaving about 6 mm of residual light pipe exposed. This stops the assistant from inadvertently advancing the light pipe too deeply into the eye. Create a handle with the label folded around the light pipe and a snap gripping the label only. From here the assistant can hold and point the light source in the direction of your choosing without getting in your way.

This technique has several advantages. It allows for bimanual dissection. It provides bright, directional light that's sometimes lacking with other chandeliers. It's voice-controlled (grunt in the general direction of the fellow). It's reversible; once you're done, remove the Luer connector and continue with the light pipe as before. And it's free.

Watch the video at
http://bit.ly/RetSpecMag-202105

6 Low-cost retinal surgery simulator

Surgical simulation training provides a low-stress environment in which to acquire and evaluate your skills. A recent systematic review concluded that vitreoretinal simulators are a useful assessment tool and may be able to teach the complex techniques required for vitreoretinal surgery.[6]

The latest retinal surgical simulators could run into the hundreds of thousands of dollars. Here, we share our experience

(Continued on page 19)

WE'RE SEEING AMAZING RESULTS. AND SO ARE THEY.

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A curious case of RAMA

An incidental exam finding upends a 70-year-old woman's back pain management plan.

By Minh Nguyen, MD, Amy Yuan, MD, and Lisa Olmos de Koo, MD, MBA

Minh Nguyen, MD

Amy Yuan, MD

Lisa C. Olmos de Koo, MD, MBA

A 70-year-old woman with a history of non-exudative age-related macular degeneration and on AREDS 2 supplementation presented to the retina service at the University of Washington for a routine follow-up. She reported that her vision had worsened in the right eye, while the left eye was stable.

She denied any floaters or flashes, or metamorphopsia. Her medical history was notable only for hypertension, well controlled on a single agent, and chronic back pain for which she had recently started taking gabapentin.

Examination findings

Best-corrected visual acuity in the right eye was 20/50, decreased from 20/30 six months earlier. Her left-eye BCVA was unchanged at 20/20. Intraocular pressures were within normal limits in both eyes. Pupils were round and equally reactive to light, and there was no afferent pupillary defect. Confrontational visual fields were full in both eyes. The anterior segment examination was notable only for stable bilateral moderate nuclear sclerosis.

The dilated fundus examination revealed confluent soft drusen and pigmentary changes in both maculae, and peripheral reticular changes in both eyes. These findings were grossly stable from her previous visit.

However, in the left eye we noted a new focal dilation of a first-order retinal arteriole at its site of division into a second-order arteriole, along with overlying focal retinal nerve fiber layer edema (*Figure 1A*).

Work-up

Optic coherence tomography and fluorescein angiography transiting the right eye were performed to evaluate both the decreased vision in the right eye as well as the vascular abnormality in the left eye. OCT demonstrated new subfoveal hyperreflective material and a small intraretinal cyst in the right eye.

FA demonstrated a small area of later leakage at the fovea, which, together with the OCT findings and objective decrease in BCVA, was consistent with new choroidal neovascular membrane (CNVM) and conversion to exudative AMD.

In the left eye, OCT showed increased peripapillary RNFL hyperreflectivity and thickness (*Figure 2A*), and FA demonstrated early brisk arterial leakage in the area

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Dr. Olmos de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington in Seattle, where Dr. Nguyen is an ophthalmology resident and Dr. Yuan is a retina fellow.

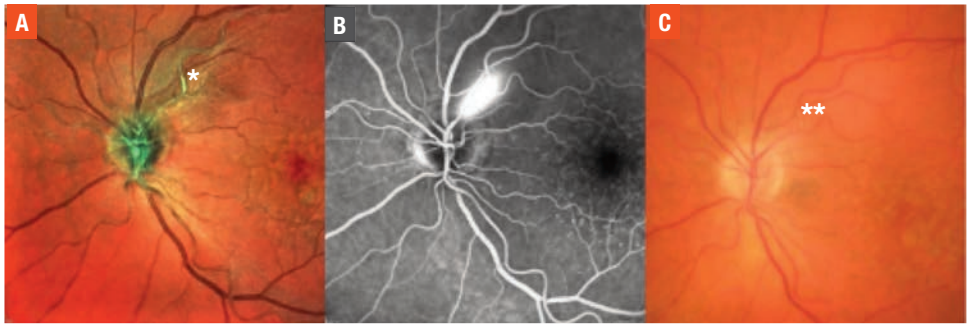


Figure 1. Fundus photography of the left eye during inversion table therapy (A) shows segmental dilation of a superotemporal arterial arcade (left of *) and surrounding retinal nerve fiber layer edema. Fluorescein angiogram of the left eye (B) shows leakage from the retinal artery microaneurysm (RAMA). Color fundus photograph (C) shows a sclerotic and calcified RAMA two months after discontinuation of inversion table therapy (left of **).

of the incidentally noted arteriole dilation (*Figure 1B*).

Diagnosis and management

For the conversion to exudative AMD in the right eye, we performed an intravitreal injection of bevacizumab. The incidental vascular findings in her otherwise asymptomatic left eye were concerning for fusiform retinal arterial microaneurysm (RAMA).

Our patient's risk factors for this condition included her age and history of hypertension, albeit well-controlled per the patient. Upon further inquiry into her recent medical history, she informed us that over the preceding month she had started to use an inversion table for five minutes every day at the recommendation of her physical therapist as a homeopathic remedy for back pain.

We hypothesized that the inversion table therapy could have episodically increased the patient's intracranial and/or blood pressure with transmittal to her retinal vasculature, and thus could be related to the formation of the new RAMA. Therefore, we advised her to stop using the inversion table and to consult with her primary-care provider to ensure optimal blood pressure control.

The patient stopped using the inversion table as instructed. At her subsequent visit one month later, the RAMA lesion appeared consolidated and calcified (*Figure 1C*), and the surrounding RNFL edema had entirely resolved on OCT (*Figure 2B*). At six-month follow-up, her vision, exam and OCT remained unchanged.

An often incidental finding

RAMA is the acquired dilation of a retinal artery, which usually develops focally at arteriovenous crossings or within the first three bifurcations of the central retinal artery.[1,2] Structurally, two types of RAMA have been described: fusiform (segmental dilation of the retinal artery); and saccular (focal outpouching of the retinal artery).[3]

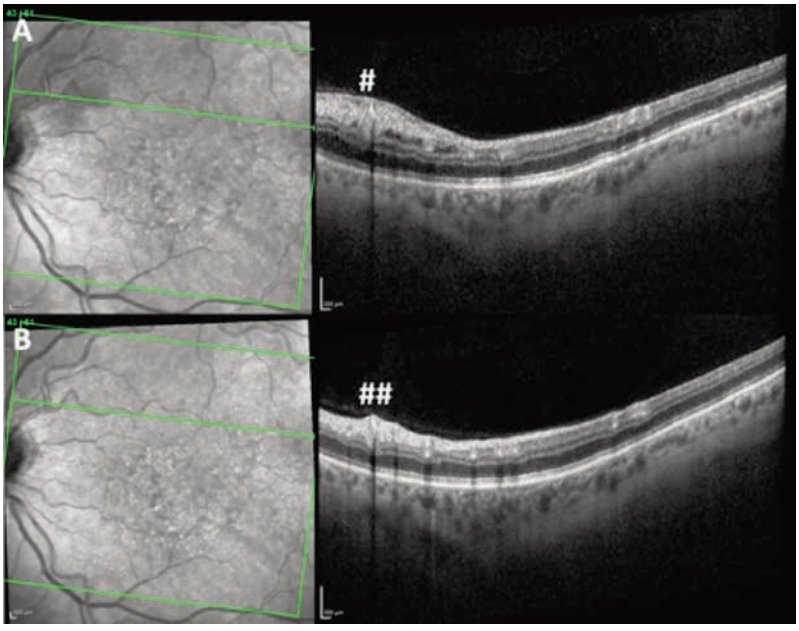


Figure 2. Optical coherence tomography of the left macula during inversion table therapy (A) shows focal retinal nerve fiber layer edema (below #). OCT of the left macula one month after discontinuation of inversion table therapy (B) shows resolved RNFL edema (below ##).

As with our patient, RAMA is often found incidentally on routine examination, and patients are usually asymptomatic.[4] However, symptoms can dramatically manifest as sequelae of aneurysm rupture.

Classically, hemorrhage in multiple layers involving the vitreous cavity, retinal laminations and subretinal space is noted on dilated fundus examination. Patients can experience significant acute vision loss.[2,5]

RAMA is highly associated with systemic hypertension and hyperlipidemia. It has been postulated that atherosclerosis and high blood pressure weaken the retinal arteriole wall, and continued hydrostatic pressure from uncontrolled hypertension leads to the formation of an aneurysm.[1,6]

As for inversion therapy

The inversion table is a modern spin on a method of antiquity to alleviate lower back pain. Hippocrates, the father of medicine, was thought to have introduced this therapy in 400 BC (*Figure 3, page 18*). He tied patients to a ladder in an upside down

Figure 3. An ancient rendering of inversion therapy using a ladder that Hippocrates was thought to have introduced in 400 BC.

position in order to treat multiple spinal diseases, including scoliosis, kyphosis, tuberculous spondylitis and dislocations of the vertebrae.[7]

In the 1980s, Robert Martin, MD, published the book *The Gravity Guiding System* and advocated for the use of gravity and the inversion table to eliminate back pain (*Figure 4*). This system theoretically works by relieving pressure on the spine, joints and muscles. With support from the physical therapy community, the public has embraced the inversion table with

Figure 4. Today's inversion therapy uses a device that the user steps into in an upright position and then tilts to the desired inversion angle.

marked enthusiasm.

Nevertheless, significantly higher systolic and diastolic blood pressure has been reported in patients who did inversion for two minutes.[8] In 2019, researchers used ultrasonography to demonstrate the significant increase in intracranial pressure (ICP) at three minutes of inversion.[9]

A separate study reported that ICP didn't return to baseline for several minutes after the study subjects resumed normal positioning. Similarly, both systolic and diastolic central retinal artery pressures of young healthy adults were shown to be significantly elevated on inversion in a study in 1983.[10]

A question worth asking

While hypertension and elevated ICP may cause serious end-organ damage such as congestive heart failure, myocardial infarction, ischemic or hemorrhagic stroke, increased retinal vessel pressure could lead to hemorrhage, and retinal artery or vein occlusion. Therefore, several authors have advised against the use of the inversion table, especially in older patients with

hypertension or a history of stroke or elevated ICP.

Ours is a case of fusiform RAMA as a manifestation of end-organ damage attributed to increased blood pressure or ICP in the setting of inversion table therapy. While our patient maintained good vision and had spontaneous involution of her aneurysm with cessation of inversion table use, the rapid development of the lesion since her normal exam six months earlier gave us cause for concern for potential worsening and rupture had she continued regular inversion.

We caution ophthalmic providers to consider inversion table therapy as a question in taking the medical history of patients who present with RAMA in the absence of other obvious risk factors, and suggest that patients consult with their primary-care providers for medical clearance before they start inversion table therapy.

Bottom line

RAMA is an acquired dilation of a retinal artery associated with hypertension and atherosclerosis. Most cases are asymptomatic and resolve spontaneously without long-term sequalae, but uncontrolled blood pressure could result in rupture and multi-layered hemorrhage.

While use of an inversion table may relieve lower back pain by taking advantage of gravity, this therapy could elevate blood pressure or ICP, resulting in serious systemic and ocular side effects, including RAMA. Older patients with cardiovascular risk factors and their providers should consider all risks and benefits when contemplating this option for the treatment of back pain.

REFERENCES

1. Rabb M, Gagliano D, Teske M. Retinal arterial macroaneurysm. Surv Ophthalmol. 1988;33:73–96.
2. Holdeman N, Le H. Retinal arterial microaneurysm. Clin Sur Ophthalmol. 2010;28:238–242.
3. Moosavi, R, Fong K, Chopdar A. Retinal artery macroaneurysms: Clinical and fluorescein angiographic features in 34 patients. Eye (Lond). 2006;20:1011–1020.
4. Bopp S. Retinal arterial macroaneurysms. In: Joussen AM, Gardner TW, Kirchhof B, Ryan SJ, eds. Retinal Vascular Disease. Springer-Verlag; New York, NY. 2007;543–560.
5. Gedik S, Gur S, Yilmaz G, Akova Y. Retinal arterial microaneurysm rupture following fundus fluorescein angiography and treatment with Nd:YAG laser membranectomy. Ophthalmic Surg Lasers Imaging. 2007;38:154–156.
6. Haskvitz E, Hanten W. Blood pressure response to inversion traction. Physical Therapy. `986;66:1361–1364.
7. Adamczyk A, Olivares G, Petito G. Retinal arterial microaneurysm: A longitudinal case study. J Am Optom Assoc. 1989;60:840–845.
8. Nalawade S, Jadhav M. A study of inversion traction therapy for lower back pain problems. Int J Engin Res Tech. 2019;8: 491–494.
9. Kondrashova T, Makar M, Proctor C, Bridgmon L, Pazdernik V. Dynamic assessment of cerebral blood flow and intracranial pressure during table tilt using ultrasonography. J Neurol Sci. 2019;404:150–156.
10. Klatz R, Goldman R, Punchuk B, Nelson K, Tarr R. The effects of gravity inversion on systemic blood pressure, intraocular pressure, and central retinal arterial pressure. J Am Optom Assoc. 1983;82:111–115.

Six frugal faves for retinal surgery

(Continued from page 14)

with a low-cost retinal simulator that was developed at the University of Cape Town by co-author Dr. Rice and colleagues.[7]

Although the model doesn't teach specific procedures, it does provide a realistic surgical environment for the trainee to explore and use real retinal instruments and learn fine motor control. It's been found to be especially useful for learning navigation and orientation with the indirect viewing system.

The model can be constructed in a few hours for less than $20 U.S. A full description of how to construct and use the model has been published online (*Figures 6A to C, page 14*).[8]

Tasks, including membrane peeling, can be mimicked by using Op-Site spray for unimanual and bimanual dissection practice. After spraying a thin layer of Op Site, you can color the membrane with a felt-tipped pen to create the impression of a stain. The membrane can be gently scored with a razor blade to create strips for peeling, or left unscored for bimanual tasks (*Figures 6D to F*).

Other tasks include threading a wire through the eye of a needle. For this exercise, fixate a pencil eraser with two sewing needles impaled into it to the bottom of the eye. A thin copper wire can then be threaded through the eyes of the needles as a one or two-handed exercise. Other advantages of this simulator include ease of accessibility and portability, which could serve well for residents and fellows as a warm-up before the start of a surgery day.

Link to the online description at
http://bit.ly/RetSpecMag-202106

REFERENCES

1. Peyman GA et al. A new wide-angle endoillumination probe for use during vitrectomy. Retina 2002;22:242.
2. E Mandelcorn et al. Unassisted scleral depression during vitrectomy surgery: Two simple, cost-effective techniques. Ophthalmic Surg Lasers Imaging Retina. 2015;46:577-578.
3. Jorge A Fortun, G Baker Hubbard 3rd. New viscodissection instrument for use with microincisional vitrectomy in the treatment of diabetic tractional retinal detachments. Arch Ophthalmol. 2011;129:352-355.
4. Iyer SSR, Regan KA, Burnham JM, Chen CJ. Surgical management of diabetic tractional retinal detachments. Surv Ophthalmol. 2019;64:780-809. [this reference isn't cited in 2nd fave]
5. Hester CC, Feldman BH. Smartphone phoneography – How to take slit lamp photographs with an iPhone. American Academy of Ophthalmology Eyewiki. Updated September 10, 2020. https://eyewiki.aao.org/Smart_Phoneography_-_How_to_take_slit_lamp_photographs_with_an_iPhone Accessed March 15, 2021.
6. Rasmussen RC, Grauslund J, Vergmann AS. Simulation training in vitreoretinal surgery: a systematic review. BMC Ophthalmol. 2019;19:90. doi: 10.1186/s12886-019-1098-x.
7. Rice JC, Steffen J, du Toit L. Simulation training in vitreoretinal surgery: A low-cost, medium-fidelity model. Retina. 2017;37:409-412.
8. Rice JC. Making a los-cost retinal surgical simulator. Community Eye Health. 2019;32:34–35.

A low-cost, one-person depressor

A technique for performing illuminated scleral depression for peripheral vitrectomy without an assistant.

By Bozho Todorich, MD, PhD

Bozho Todorich, MD, PhD

Bios

Dr. Todorich is with Lehigh Eye Specialists, Allentown, Pennsylvania.

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

DISCLOSURES:
Dr. Todorich disclosed relationships with Vortex Surgical, Genentech, Regeneron Pharmaceuticals and Allergan/AbbVie.

Dr. Hahn disclosed serving as a consultant to DORC.

Advances in vitrectomy platforms have automated most parts of vitrectomy surgery so that surgeons can perform critical steps, such as fluid-air exchange, silicone-oil injection or laser retinopexy efficiently and independently.

Yet, for peripheral vitrectomy, particularly in primary retinal detachment repair, many of us still use assistants to do scleral indentation. For surgeons in private practice or non-academic institutions, this can be particularly challenging, because assistants aren't always available. In those cases, retina surgeons may forgo depressed vitreous base shaving or resort to chandelier illumination, which is more expensive.

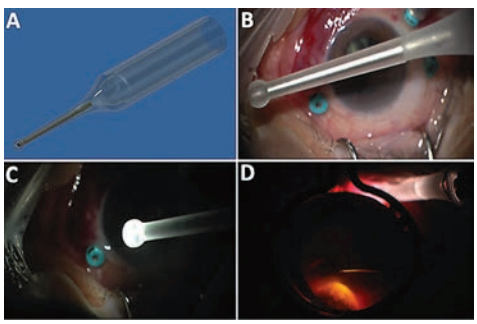
A low-cost depressor cap

A low-cost, disposable depressor cap (*Figure A*) compatible with Alcon and Bausch + Lomb light pipes is available from Vortex Surgical. An analogous depressor is available for the DORC Eva system.

The light pipe is inserted in the depressor, which is molded in the shape of a traditional ball-point depressor (*Figure B*), thus emitting light through the tip that allows for simultaneous depression, transillumination and peripheral vitrectomy (*Figures C, D*).

For optimal illumination, the light pipe setting is set to maximum on the vitrectomy machine. The tip is made of polished polycarbonate, which maximizes light transmission and allows it to slide into the conjunctival fornix and glide along the scleral surface.

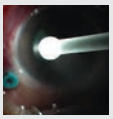
The shaft of the depressor is fortified with a metal hypodermic needle that enhances stiffness and prevents glare from light backscatter. The device accommodates 23-, 25- and 27-gauge instruments.



The depressor cap (A) converts any 23- to 27-gauge light pipe into a scleral depressor-transilluminator. The light pipe is inserted with the tip fully seated within the ballpoint end (B) and with the light on (C). Intraoperative view (D) of "task-specific" illumination for simultaneous vitreous base shaving.

View the Video

Dr. Todorich demonstrates his novel illumination technique for one-person retinal detachment repair. Available at http://bit.ly/VideoPearl_022



Ideal cases for the depressor

The depressor performs best with lightly pigmented and/or myopic eyes with thin sclera, which permit the most light penetration. In these eyes, effective depression-transillumination can be visualized on any conventional microscope.

In more pigmented eyes or cases with vitreous hemorrhage, a digital microscope, such as the Alcon Ngenuity 3D system that can amplify low-level luminance, can enhance dimmer and more challenging viewing. The vitreous isn't as well visualized as with conventional endoillumination, so you should methodically shave clock hour by clock hour to avoid skip areas, and use adjuvants such as triamcinolone if you need it to enhance the Tyndall effect of the peripheral vitreous.

If you're using a digital microscope, you can further improve the view of the vitreous by manipulating the light and color settings. The learning curve consists of about a dozen or so cases to get used to "task specific" rather than diffuse conventional endoillumination, as the video demonstrates, and to train your hands to follow each other in both pseudophakic and phakic eyes.

This low-cost device converts any light pipe into a depressor-transilluminator, which gives you complete and independent control of peripheral vitrectomy. RS

"I was only seeing light flashes early on, but light FLASHES when you've not seen anything for so many years—it was wonderful"

—Keith H, retinal prosthesis recipient

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Ocular gene therapy: The next generation

Emerging viral and synthetic vectors along with newer delilvery platforms are poised to broaden genetic treatments in retina.

Jaycob Avaylon, BS

Glenn Yiu, MD, PhD

By Jaycob Avaylon, BS, Glenn Yiu, MD, PhD

Take-home points

- Ocular gene therapies show promise for treating both inherited and acquired retinal diseases through gene replacement and biofactory approaches.
- New generations of viral capsids and synthetic nanoparticles can improve the efficacy and carrying capacity of gene-delivery vectors while reducing immunogenicity and the risk of mutagenesis.
- Innovations in surgical techniques and vector-delivery methods such as transscleral and suprachoroidal catheter-based microneedles are improving the ease and biodistribution of gene-delivery vectors.

Bios

Mr. Avaylon is a second-year medical student at California Northstate University College of Medicine in Elk Grove.

Dr. Yiu is an associate professor at the University of California, Davis, in Sacramento, where he's a vitreoretinal surgeon and clinician-scientist. His research interests include gene therapy and gene editing, ocular imaging and age-related macula degeneration.

DISCLOSURES: Mr. Avaylon has no relevant financial disclosures.

Dr. Yiu is a consultant to Allergan, Alimera Sciences, Carl Zeiss Meditec, Clearside Biomedical, Genentech, Gyroscope Therapeutics, Intergalactic Therapeutics, Iridex, Topcon and Verily. He also disclosed receiving research support from Clearside, Genentech and Iridex.

Ocular gene therapy is emerging as a potentially disruptive technology in the management of inherited and acquired retinal conditions.[1-4] The term gene therapy broadly encompasses gene replacement strategies to replace nonfunctional genes with normal copies in inherited retinal diseases, biofactory approaches to generate soluble proteins such as anti-VEGF biologic agents for age-related macular degeneration and emerging gene-editing tools to modify gene expression at the DNA level.[2-4]

The mainstay of these therapies involves intraocular delivery of viral vectors that can carry the therapeutic gene into the nuclei of target cells. The choice of vector and route of administration are critical determinants of the efficacy and safety of these delivery platforms, and recent advances are broadening the range of options available.

Delivery vectors

Viral vectors leverage the natural ability of these microorganisms to infect and transport genetic material into host cells. The effectiveness of a gene-delivery vector is determined by high expressivity, large transgene-carrying capacity, long durability, low immunogenicity and low risk of mutagenicity.

Adenoviruses were among the first used for gene therapy due to their high infectivity and large capacity, but they've largely been abandoned due to their strong immunogenicity and short duration of expression.[5]

Lentiviruses are a subtype of retroviruses including HIV that also have high infectivity and a large carrying capacity. However, because they naturally integrate into host genomes, they carry an increased risk of mutation and oncogenesis.[6]

Adeno-associated viruses emerge

By contrast, adeno-associated viruses (AAVs) are the most common viral vector used for ocular gene therapy due to their ability to transduce multiple retinal cell types, low pathogenicity and low risk of

mutations because they don't integrate into the host genome.[7]

Different serotypes of AAV capsids provide different tropisms for different retinal cell types. For example, intravitreal AAV2 and AAV8 can target retinal ganglion cells, while AAV2, AAV5, AAV7, AAV8 and AAV9 can transduce photoreceptors and RPE cells when given subretinally.[7]

The first Food and Drug Administration-approved ocular gene therapy, voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), uses an AAV2 vector to deliver a functional copy of the *RPE65* gene for the treatment of Leber congenital amaurosis type 2.[8] Other retinal conditions for which AAV gene therapies are under investigation include choroideremia, achromatopsia, X-linked retinitis pigmentosa, X-linked retinoschisis and AMD.

Expanding use of viral vectors

New advances are also being investigated to expand the use of viral vectors. AAVs have a limited capacity and can only carry genes smaller than 4.7kb. Therefore, larger genes, such as the *ABCA4* gene (6.8kb) in Stargardt disease, must rely on lentivirus or nonviral vectors for effective delivery.[9]

To overcome this limitation, larger genes could be split in half and delivered with dual AAV vectors, then reconstituted in host cells by exploiting natural mechanisms of rejoining DNA such as splicing or homologous recombination.[10] Efforts are also ongoing to engineer non-integrating lentiviruses to minimize the risk of mutagenesis.[11]

Finally, newer generations of AAV have been designed to overcome natural ocular barriers. Typically, AAV vectors for retinal gene therapies must be delivered by subretinal injections because viral particles in the vitreous cavity are prevented from reaching photoreceptors and retinal pigment epithelium by the internal limiting membrane.

New AAV capsids such as the *AAV2.7m8* have been developed using methods known as *in vitro* "directed evolution" which can overcome the ILM barrier and transduce the retina, even when they're administered intravitreally.[12] The Phase I OPTIC Trial is evaluating intravitreal ADVM-022 (Adverum Biotechnologies), an *AAV2.7m8* to deliver aflibercept for treatment of anti-VEGF-responsive neovascular AMD (ClinicalTrials.gov NCT03748784).

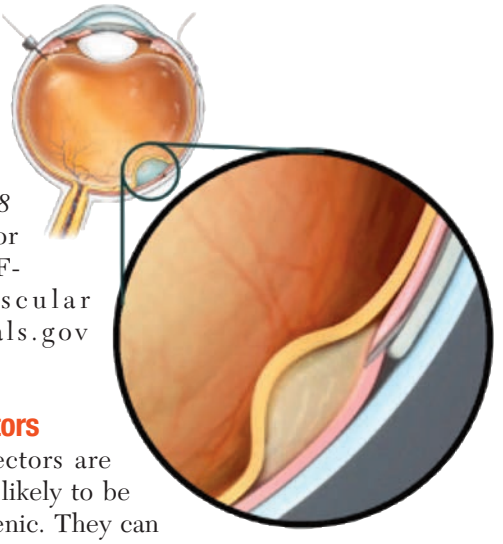

Figure 1: A subretinal delivery system using a microneedle deployed from a suprachoroidal catheter can access the subretinal space without creating a retinotomy. *(Courtesy Gyroscope Therapeutics)*

Non-viral delivery vectors

Non-viral delivery vectors are nonpathogenic and less likely to be immunogenic or mutagenic. They can be engineered with a very large carrying capacity (20kb), but are also generally less effective and less durable for gene transduction. Emerging nonviral technologies include synthetic polymers and nanoparticles, lipid-based delivery systems and cell penetrating peptides.[13]

DNA nanoparticles have been evaluated in early clinical trials for cystic fibrosis, and in preclinical studies for retinitis pigmentosa, LCA and Stargardt disease in mouse and rabbit models,[13-15] with studies demonstrating stable expression up to two years in mice.[14]

Some portions of the eye may also be amenable to electroporation—the use of an electric field to create temporary pores in cell membranes to allow DNA uptake. Electroporation of DNA plasmids into ciliary muscles can serve as a bio-factory for therapeutic proteins (Eyevensys) and appears effective in animal models of uveitis, RP and wet AMD for up to six months.[16] This platform is undergoing clinical trials for non-infectious uveitis (ClinicalTrials.gov NCT03308045).

Delivery methods

Unlike intravitreal injections, which can be readily performed by retina specialists in office settings, subretinal injections require vitreoretinal surgery and are

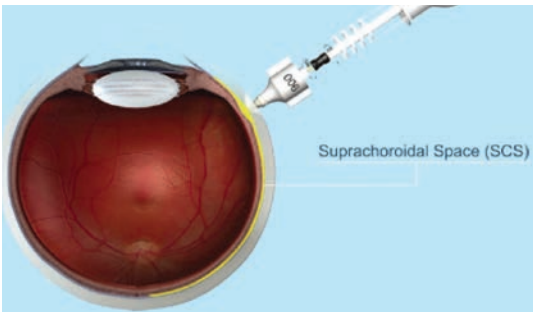

Figure 2: A transscleral microneedle can be used to deliver drugs or viral vectors to the suprachoroidal space. *(Courtesy Clearside Biomedical)*

susceptible to complications associated with vitrectomy and creation of a subretinal bleb, especially in eyes with IRDs where retinal tissues may be more atrophic and fragile. In one of the gene therapy trials for choroideremia, a patient developed intraretinal and subretinal hemorrhage during the injection procedure, resulting in localized atrophy and severe vision loss.[17]

Strategies to mitigate these surgical complications include the use of a saline "prebleb" to confirm successful size, location, and retinal elevation of the therapeutic region; automated viscous fluid injection rather than manual depression of the syringe plunger; and intraoperative optical coherence tomography (iOCT) for real-time visualization. More recent clinical trials for choroideremia that use iOCT have reported fewer complications than earlier studies.[18]

Other anecdotal surgical pearls include use of a subretinal air bubble, air tamponade and supine postoperative positioning.

Despite the potential surgical complications, subretinal injections remain the most effective route for transducing the outer retina as they overcome the ILM barrier.

The most effective route

Despite the potential surgical complications, subretinal injections remain the most effective route for transducing the outer retina as it overcomes the ILM barrier. Another major advantage is the immune privilege of the subretinal space.[19,20] Preclinical animal studies and human trials have reported significantly higher rates of ocular inflammation after intravitreal compared with subretinal AAV injections.[19]

It appears that AAV in the vitreous cavity readily escapes into circulation through trabecular outflow, prompting a host immune response that can trigger both intraocular inflammation and adaptive immunity against future AAV delivery, which have been reported in patients who require a second eye treatment.[21-23]

Cases of intraocular inflammation after subretinal gene therapies are believed to arise from reflux or leakage of virus into the vitreous. This concern may be overcome with an innovative subretinal delivery system (Orbit SDS, Gyroscope Therapeutics) that uses a flexible canula inserted through the suprachoroidal space, accessed via a surgical sclerotomy (*Figure 1, page 23*). This system can deploy a microneedle that punctures through the choroid to access the subretinal space for vector delivery, thus avoiding the vitrectomy and retinotomy required for transvitreal subretinal delivery.

The ongoing FOCUS phase I/II clinical trial aims to evaluate an investigational AAV-based complement factor I (CFI) gene therapy (GT005) administered with this system in patients with geographic atrophy, and will enable a comparison between subretinal delivery and transvitreal methods (ClinicalTrials.gov NCT03846193).[24,25]

Suprachoroidal injection

A novel ocular gene delivery route involves accessing the suprachoroidal space. Suprachoroidal injection of a triamcinolone acetonide suspension using trans-scleral microneedles has demonstrated safety and efficacy for macular edema due to noninfectious uveitis in a Phase III trial (*Figure 2*).[26] The injections enabled targeted delivery of drug to the posterior pole while minimizing adverse effects on anterior segment tissue.

Like intravitreal injections, this method can be given in an office setting. Suprachoroidal delivery of AAV in pigs and nonhuman primates enabled widespread gene expression in the posterior pole, although the cellular tropism and pattern of expression differed between studies, including those from our own group.[27]

Due to its location outside the blood-retinal barrier, suprachoroidal AAV delivery has a potential risk of immunogenicity, although our studies employed a green fluorescent protein transgene that's foreign to primates.[28] Suprachoroidal injections of an AAV that expresses a native or humanized protein should reduce the risk of inflammation, as shown in new Phase I/II studies evaluating suprachoroidal delivery of RGX-314 (RegenXbio), an AAV8 encoding a ranibizumab-like anti-VEGF protein for neovascular AMD (ClinicalTrials.gov NCT04567550).

Suprachoroidal delivery of DNA nanoparticles is also under preclinical investigation and could minimize the immunogenicity associated with viral vectors.[15,29]

Bottom line

Ocular gene therapy is a promising and emerging field with the potential to treat both rare IRDs and more common acquired retinal conditions. Newer generations of viral and synthetic vectors may improve expressivity and carrying capacity while reducing immunogenicity and mutagenicity. Advances in surgical and delivery methods are improving the ease of vector administration and biodistribution of gene expression. The choice of vector and route of delivery depends on the disease and transgene, as well as target location and cell types.

Gene replacement or editing therapies for IRDs may require more accurate vector delivery to specific cell types through subretinal injections, while biofactory approaches may benefit from easier, less invasive strategies to rival existing therapies. A number of exciting ongoing clinical trials will provide important insight into the potential of these novel technologies to widen the doors for ocular gene therapy. RS

REFERENCES

1. Benati D, Patrizi C, Recchia A. Gene editing prospects for treating inherited retinal diseases. J Med Genet. 2020;57:437-444.
2. Bordet T, Behar-Cohen F. Ocular gene therapies in clinical practice: viral vectors and nonviral alternatives. Drug Discov Today. 2019;24:1685-1693.
3. Moore NA, Morral N, Ciulla TA, Bracha P. Gene therapy for inherited retinal and optic nerve degenerations. Expert Opin Biol Ther. 2018;18:37-49.
4. Chung SH, Frick SL, Yiu G. Targeting vascular endothelial growth factor using retinal gene therapy. Ann Transl Med 2020. doi:10.21037/atm-20-4417
5. Lee CS, Bishop ES, Zhang R, et al. Adenovirus-mediated gene delivery: Potential applications for gene and cell-based therapies in the new era of personalized medicine. Genes Dis. 2017;4:43-63.
6. Milone MC, O'Doherty U. Clinical use of lentiviral vectors. Leukemia. 2018;32:1529-1541.
7. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. Nat Rev Drug Discov. 2019;18:358-378.
8. Miraldi Utz V, Coussa RG, Antaki F, Traboulsi EI. Gene therapy for RPE65-related retinal disease. Ophthalmic Genet. 2018;39:671-677.
9. Auricchio A, Trapani I, Allikmets R. Gene therapy of ABCA4-associated diseases. Cold Spring Harb Perspect Med. 2015;5:a017301.
10. Trapani I, Colella P, Sommella A, et al. Effective delivery of large genes to the retina by dual AAV vectors. EMBO Mol Med. 2014;6:194-211. doi:10.1002/emmm.201302948
11. Hamilton AM, Foster PJ, Ronald JA. Evaluating nonintegrating lentiviruses as safe vectors for noninvasive reporter-based molecular imaging of multipotent mesenchymal stem cells. Hum Gene Ther. 2018;29:1213-1225.
12. Dalkara D, Byrne LC, Klimczak RR, et al. In vivo-directed evolution of a new adeno-associated virus for therapeutic outer retinal gene delivery from the vitreous. Sci Transl Med. 2013;5:189ra76.
13. Adijanto J, Naash MI. Nanoparticle-based technologies for retinal gene therapy. Eur J Pharm Biopharm. 2015;95:353-367.
14. Han Z, Conley SM, Makkia R, Guo J, Cooper MJ, Naash MI. Comparative analysis of DNA nanoparticles and AAVs for ocular gene delivery. PLoS One. 2012;7:e52189.
15. Kansara VS, Cooper M, Sesenoglu-Laird O, Muya L, Moen R, Ciulla TA. Suprachoroidally delivered DNA nanoparticles transfect retina and retinal pigment epithelium/choroid in rabbits. Transl Vis Sci Technol. 2020;9:21.
16. Bigot K, Gondouin P, Bénard R, et al. Transferrin non-viral gene therapy for treatment of retinal degeneration. Pharmaceutics. 2020;12:836.
17. Dimopoulos IS, Hoang SC, Radziwon A, et al. Two-year results after aav2-mediated gene therapy for choroideremia: The Alberta experience. Am J Ophthalmol. 2018;193:130-142.
18. Lam BL, Davis JL, Gregori NZ, et al. Choroideremia gene therapy Phase 2 clinical trial: 24-month results. Am J Ophthalmol. 2019;197:65-73.
19. Nuzbrokh Y, Kassotis AS, Ragi SD, Jauregui R, Tsang SH. Treatment-emergent adverse events in gene therapy trials for inherited retinal diseases: A narrative review. Ophthalmol Ther. 2020;9:709-724.
20. Yiu G, Chung SH, Mollhoff IN, et al. Suprachoroidal and subretinal injections of AAV using transscleral microneedles for retinal gene delivery in nonhuman primates. Mol Ther Methods Clin Dev. 2020;16:179-191.
21. Seitz IP, Michalakis S, Wilhelm B, et al. Superior retinal gene transfer and biodistribution profile of subretinal versus intravitreal delivery of AAV8 in nonhuman primates. Invest Ophthalmol Vis Sci. 2017;58:5792-5801.
22. Reichel FF, Peters T, Wilhelm B, et al. Humoral immune response after intravitreal but not after subretinal AAV8 in primates and patients. Invest Ophthalmol Vis Sci. 2018;59:1910-1915.
23. Kotterman MA, Yin L, Strazzeri JM, Flannery JG, Merigan WH, Schaffer DV. Antibody neutralization poses a barrier to intravitreal adeno-associated viral vector gene delivery to non-human primates. Gene Ther. 2015;22:116-126.
24. de Smet MD, Lynch JL, Dejneka NS, Keane M, Khan IJ. A subretinal cell delivery method via suprachoroidal access in minipigs: Safety and surgical outcomes. Invest Ophthalmol Vis Sci. 2018;59:311-320.
25. Heier JS, Ho AC, Samuel MA, et al. Safety and efficacy of subretinally administered palucorcel for geographic atrophy of age-related macular degeneration: Phase 2b study. Ophthalmol Retina. 2020;4:384-393.
26. Yeh S, Khurana RN, Shah M, et al. Efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: Phase 3 randomized trial. Ophthalmology. 2020;127:948-955.
27. Ding K, Shen J, Hafiz Z, et al. AAV8-vectored suprachoroidal gene transfer produces widespread ocular transgene expression. J Clin Invest. 2019;129:4901-4911.
28. Chung SH, Mollhoff IN, Mishra A, et al. Host immune responses after suprachoroidal delivery of AAV8 in nonhuman primate eyes. Hum Gene Ther. Published online January 15, 2021.
29. Kansara V, Muya L, Wan CR, Ciulla TA. Suprachoroidal delivery of viral and nonviral gene therapy for retinal diseases. J Ocul Pharmacol Ther. 2020;36:384-392.

Suprachoroidal delivery of DNA nanoparticles is also under preclinical investigation and could minimize the immunogenicity associated with viral vectors.

How COVID-19 has altered uveitis management

The pandemic has potentially changed the risk-benefit balance between local therapy and systemic immunosuppression.

Dilraj Grewal, MD

By Dilraj Grewal, MD

Take-home points

- The COVID-19 pandemic has disrupted care patterns as missed visits have led to the potential for significant disease progression in some patients with noninfectious posterior uveitis.
- Uveitis patients may be at higher risk than the general population of contracting COVID-19 or suffering a more severe course of the virus.
- The current consensus is that most posterior uveitis patients who are well-managed on systemic immunosuppressive therapy should continue their current management.
- The American College of Rheumatology has developed guidelines for patients on immunosuppression when they receive the COVID-19 vaccine.

The COVID-19 pandemic has disrupted care patterns and led to potential disease management changes across many therapeutic areas. Early on, ophthalmology was one of the most affected specialties in medicine, with some practices severely curtailed for about two months, doing only the most urgent procedures. For example, Italian researchers reported an 86-percent reduction in outpatient treatment for posterior uveitis in spring 2020 compared to the prior year.[1]

Even now, although clinics have reopened and vaccinations are ramping up, challenges still exist in getting our patients to the clinic, and widespread vaccination is still a few months away. Younger patients may have children at home and find it more difficult than usual to get away. Older patients who live in assisted-living or a skilled-nursing facility may still have strict requirements for leaving or returning to their community. Others simply remain very fearful. Some have opted to delay care to avoid leaving home. Unfortunately, these delays have led to some cases of disease progression.

Even as more people get vaccinated, some of these precautions should stay in place because it's going to take months before we reach herd immunity and our offices are up and running at full capacity.

Diagnostic protocols

For all of our known or potential uveitis patients entering the clinic, awareness of COVID-19 status is important. Justine Smith, MBBS, PhD, and Timothy Y.Y. Lai, MD, in Australia recommended as of last May avoiding aerosol-generating diagnostic procedures that pose a high risk of viral transmission.[3] For example, they suggest that diagnostic bronchoscopy is unnecessary if the presentation is otherwise consistent with ocular sarcoidosis. Lower-risk diagnostic procedures can be planned in collaboration with internist colleagues.

Vitrectomy is no longer contraindicated in COVID-negative patients. In COVID-

Bio
Dr. Grewal is a vitreoretinal and uveitis specialist at Duke Health in Durham, North Carolina.

DISCLOSURE: Dr. Grewal disclosed acting as a consultant to Allergan/AbbVie, Clearside Biomedical, DORC and EyePoint Pharmaceuticals.

positive patients, full personal protective equipment should be worn, and a COVID-specific operating room used for essential diagnostic or surgical procedures.[2]

In the clinic, we follow Centers for Disease Control and Prevention guidelines, including phone prescreening, limiting waiting room times, social distancing, mandatory masks, slit lamp shields, enhanced cleaning of the room and equipment between patients, and universal COVID testing for surgical patients. In some cases, we've been able to switch to telemedicine visits, but that can be quite challenging for retinal conditions, including posterior uveitis.

Virus risk and uveitis patients

It's important to note that noninfectious posterior uveitis patients are predisposed to autoimmune issues and may be at higher risk than the general population of suffering a more severe course of the virus.[3,4] It's possible that an overactive immune system could be prone to the so-called cytokine storm that's been associated with severe cases of COVID-19. We know that interleukin-6 (IL-6) is upregulated in COVID-19, as well as in some uveitic conditions.

Additionally, management of posterior noninfectious uveitis often involves suppression of the immune system with steroids or immunomodulatory agents. Pre-pandemic, clinicians advised uveitis patients on systemic treatments to be careful with hand-washing and avoid exposure to sick people. Precautions are even more important now.[3]

Discussion of treatment options

Increasingly, a consensus has emerged that posterior uveitis patients well-managed on systemic immunosuppressive therapy should continue their current management while taking all recommended precautions.[2,3,5,6] However, we must also take the patient's lifestyle and preferences into consideration.

Even as vaccines roll out, the care of patients on immunosuppression therapy remains a concern. The American College of Rheumatology has issued guidelines for managing patients on immunosuppression receiving the COVID-19 vaccine.[7] Medications such as methotrexate should be withheld for one week after each vaccine dose, whereas others, such as mycophenolate, azathioprine or steroids, don't require any modification.

If the patient is apprehensive about immunosuppression, a discussion on alternatives is warranted. In most cases, the risk of a flareup with discontinuation or weaning off the systemic medication, combined with the additional office visits associated with a change in management, may counterbalance the risk of contracting COVID-19. However, for some patients who have already contracted pneumonia or another infection, or for those at very high risk of exposure (for example, health-care workers or those with jobs that require high levels of public contact), we may alter the risk assessment.

In general, we need to weigh not only the patient's current therapy and uveitis severity,

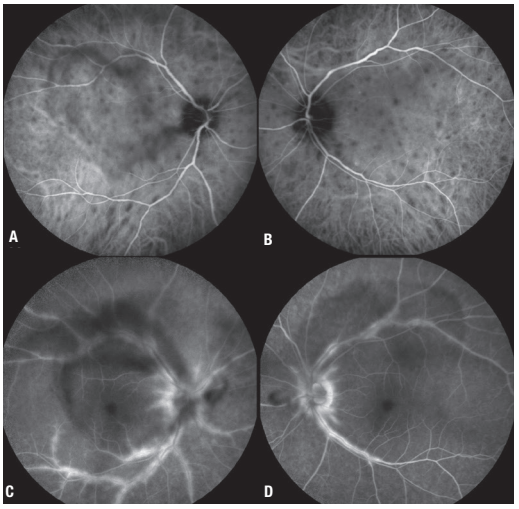

Figure 1. Indocyanine green angiography (A, B) shows multiple round-to-oval hypocyanescent choroidal lesions throughout the posterior pole in a 40-year-old woman with birdshot chorioretinitis. Disease activity persisted despite adalimumab 40 mg (Humira, AbbVie) monotherapy q2w. Fluorescein angiography (C, D) shows significant posterior pole perivascular leakage with visible vitreous opacities consistent with vitreous inflammation. After offering her the options of a second immunosuppressive agent or local therapy, she opted for the latter.

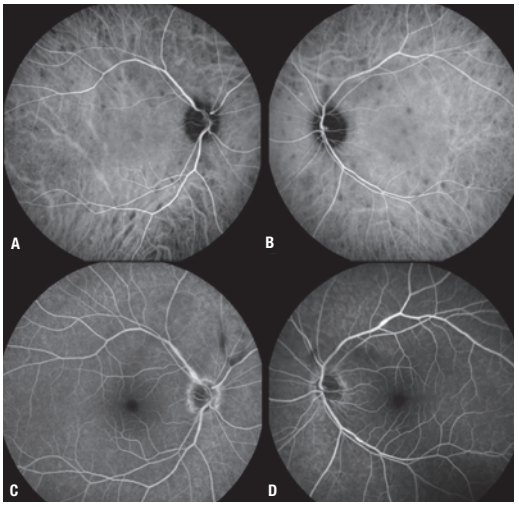

Figure 2. Three months after we added the fluocinolone acetonide intravitreal implant 0.18 mg in both eyes of the patient in Figure 1, fluorescein angiography demonstrates significant reduction in the size and number of the hypocyanescent lesions (A, B) and near complete resolution of perivascular leakage, along with much improved vitreous inflammation (C, D).

but also their ocular and systemic comorbidities, age, lens status and personal preferences. Patients with underlying conditions such as lupus, rheumatoid arthritis or sarcoidosis will likely be best served by maintaining immunosuppression, because it treats their systemic and ocular problems.

Who merits a change in approach

In my practice, there are two distinct groups of patients for whom I consider a change in approach to reduce or avoid immunosuppression. The first is the newly diagnosed patient or one who isn't completely controlled on their current immunosuppressive therapy and for whom I would normally be adding an additional immunosuppressive agent. In these patients, supplementation with local steroid therapy may help delay or avoid additional immunosuppression.[3,5,6] Figures 1 and 2 (*page 25*) illustrate such an example.

The second group is those who require multiple immunosuppressive agents only for the eye and are concerned about the amount of immunosuppression. I discuss with them the possibility of reducing the burden of immunosuppression. Perhaps we take away one of the immunosuppressive agents and, if ocular comorbidities allow, supplement with a local steroid therapy.

Local steroid therapy will cause a cataract, which is a concern in a young patient who still has accommodation, especially if both eyes are involved and would require bilateral injections.

In older patients in the later stages of presbyopia, cataract development is less of a concern. We also have to consider the risk of a steroid response with an intraocular pressure elevation, especially if the patient already has glaucoma.

Sustained-release options

Once it has been determined that the patient has chronic noninfectious posterior uveitis, it's important to explain that the goal of treatment is sustained control of inflammation. We know that fluctuations in inflammatory activity can produce a yo-yo effect in which after the uveitis flares up and subsides, vision doesn't necessarily return to baseline. With each flare-up, the patient may lose some visual quality or visual function, with the potential for significant cumulative decline over time. Sustained-release (SR) local steroid therapy offers the potential to achieve a steady state in uveitis control.

SR ophthalmic drug delivery has been an important focus over the past several years because there's such a high need— not only in uveitis, but in conditions such as macular degeneration, retinal vein occlusion, glaucoma and diabetic macular edema.

The first SR steroid technology in ophthalmology was the fluocinolone-releasing Retisert (Bausch + Lomb). It has the advantage of a long duration of effect (three years), but it must be implanted surgically in the operating room, with a large incision and sutures. Additionally, while Retisert is very powerful at reducing inflammation, it causes cataract and has a high rate of IOP elevation.

Next-generation platforms

As SR technology has continued to advance, the drug reservoirs have become much smaller and can be injected in the office. The first such implant was Ozurdex (Allergan/AbbVie), a rice-grain-sized, bioerodible pellet that releases dexamethasone for three to six months.

More recently, we have a new SR technology, Yutiq (EyePoint Pharmaceuticals), that's approved to treat posterior noninfectious uveitis. It combines the durability of Retisert and the convenience of an in-office procedure like Ozurdex, with less IOP elevation than Retisert.[8,9]

Yutiq has about one third of the fluocinolone of Retisert (0.18 mg vs. 0.59 mg), and the slow release provides a sustained anti-inflammatory effect over three years, with much lower risk of IOP rise and cataract formation due to the lower dose.[8,9]

With each flare-up, the patient may lose some visual quality or function, with the potential for significant cumulative decline over time. Sustained-release local steroids offer the potential for steady control.

This profile makes it a good potential choice for those uveitis patients who would like to delay or reduce immunosuppression during the pandemic.

Precautionary pre-insertion steps

In a patient who has never received a local steroid injection, I prefer to first evaluate their response to a single short-acting steroid injection, in terms of both efficacy and tolerability, before proceeding with an SR insert. In addition to evaluating for an increase in IOP, it also helps to confirm that the patient is responding well to the steroid. The injection provides a bolus of steroid that can rapidly reduce the macular edema, if present. This can be followed with an SR implant to keep the edema and uveitis controlled over the long term.

It's important to recognize that local therapy isn't a good choice for some patients, including those with very severe, sight-threatening inflammation along with systemic inflammation that requires immediate control; pediatric patients; those with uncontrollable IOP elevation; and patients with severe glaucoma who can't tolerate any pressure increase.

Bottom line

In most patients, the risk of uveitis disease progression with no treatment or undertreatment is much greater than the risk of contracting COVID-19. It's our role to help patients understand their relative risks and to responsibly weigh all the factors that go into decision-making for the management of uveitis, including comorbidities and patient preferences.

Even as the pandemic subsides, it may make sense to delay or reduce the burden of systemic immunosuppression for some patients. In these cases, local therapy with SR steroids can be a very effective tool. Of course. no treatment is perfectly safe and effective. For this reason, we must always be prepared to make adjustments and reassess the risks for our patients.

Pros and cons of immunosuppressive vs. local therapy for posterior uveitis

Treatment	Pros	Cons
Systemic immunosuppression	• Addresses both uveitis and underlying systemic conditions. • Treats both eyes at once. • Achieves steady state dosing.	• Requires ongoing monitoring of liver and kidney function and blood counts. • May increase risk of infections. • Often not suitable for women of childbearing age. • May cause side effects including nausea, gastrointestinal issues or other problems.
Local therapy	• Doesn't require systemic immunosuppression. • Treatment is targeted to the eyes (for those who only have uveitis without systemic involvement). • Can maintain steady control with sustained-release therapies. • Reduces total number of patient encounters and need for blood work.	• Risk of early cataract formation, intraocular pressure elevation, endophthalmitis and retinal detachment. • Patients may need injections/implants in both eyes.

REFERENCES

1. Borrelli E, Grosso D, Vella G, et al. Impact of COVID-19 on outpatient visits and intravitreal treatments in a referral retina unit: Let's be ready for a plausible "rebound effect." Graefes Arch Clin Exp Ophthalmol. 2020;258:2655-2660.
2. Smith JR, Lai TYY. Managing uveitis during the COVID-19 pandemic. Ophthalmology. 2020;127:e65-67.
3. Agarwal R, Testi I, Lee CS, et al. Evolving consensus for immunomodulatory therapy in non-infectious uveitis during the COVID-19 pandemic. Br J Ophthalmol. Published online June 25, 2020. doi: 10.1136/bjophthalmol-2020-316776.
4. International Uveitis Study Group, Foster Ocular Inflammation Society and International Ocular Inflammation Society. Evolving consensus experience of the IUSG-IOIS-FOIS with uveitis in the time of COVID-19 infection. April 3, 2020. https://www.iusg.net/uploads/images/IUSG%20Library/v004-consensus-experience-document.pdf. Accessed November 11, 2020.
5. Hung JCH, Li KKW. Implications of COVID-19 for uveitis patients: Perspectives from Hong Kong. Eye 2020;34:1163-1164.
7. Agarwal AK, Sudharshan S, Mahendradas P, et al. Impact of COVID-19 pandemic on uveitis patients receiving immunomodulatory and biological therapies (COPE Study). Br J Ophthalmol. Published online October 3, 2020. doi: 10.1136/bjophthalmol-2020-317417.
7. COVID-19 vaccine glinical guidance summary for patients with rheumatic and muscoloskeletal diseases. American College of Rheumatology. https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf. Updated February 8, 2021.
8. Jaffe GJ, Pavesio CE, Study investigators. Effect of a fluocinolone acetonide insert on recurrence rates in noninfectious intermediate, posterior, or panuveitis: Three-year results. Ophthalmology 2020;127:1395-1404.
9. Eyepoint Pharmaceuticals. Full prescribing information. Yutiq.com. https://eyepointpharma.com/wp-content/uploads/2019/01/YUTIQ-USPI-20181120.pdf. Accessed December 2, 2020.

AI in retina: Ready for prime time?

Artificial intelligence is ready to be incorporated into retina referral networks. Here's a look at the state of the science.

Grayson W. Armstrong, MD, MPH

Grayson W. Armstrong, MD, MPH

Take-home points

- Multiple artificial intelligence-based devices have entered clinical practice and are capable of autonomous detection of diabetic retinopathy.
- Clinical research into AI applications of retinal imaging has grown exponentially in recent years, although commercial applications of these technologies is lagging behind.
- Retina specialists, primary-care providers and patients can benefit from novel AI technologies implemented into existing clinical workflows and referral networks.
- We should carefully evaluate patient privacy and regulatory considerations before implementing novel AI technologies.

Artificial intelligence has received considerable attention for its promise and potential in advancing the field of retina, and for good reason. There have been remarkable breakthroughs in the last few years in the use of AI to screen for, diagnose, triage and grade ophthalmic disease. This has culminated in Food and Drug Administration approval of two autonomous AI devices meant to screen for diabetic retinopathy.

Additional AI-based retinal diagnostics are under investigation and stand to enter the U.S. market in the near future. What's more, AI has been applied to the detection of systemic disease through the use of ophthalmic imaging.

While research applications of AI continue to advance at breakneck speeds, clinical uptake is proceeding at a more metered pace. Ultimately, retina specialists, when looking to implement AI in their practices or referral networks, must consider issues related to patient and physician perceptions of AI, privacy concerns and practical considerations such as billing and regulation.

What AI is

AI is a type of engineering that allows computers to perform intelligent functions. Machine learning (ML) is a subset of AI that enables computers to evaluate and learn from a set of data and subsequently perform a task to autonomously classify future data and draw conclusions about the data. The performance of an ML algorithm can be evaluated using metrics such as sensitivity, specificity, accuracy and area under the receiver operating characteristic (AUROC).

Clinical images are particularly useful to input as data into ML models and often require specific types of ML algorithms, known as convolutional neural networks (CNNs), to evaluate the images and make conclusions. CNNs operate like the complex neuronal synapses in the brain or retina.

Bio
Dr. Armstrong is a physician and surgeon at Massachusetts Eye and Ear and an instructor in ophthalmology at Harvard Medical School, Boston.

DISCLOSURE:
Dr. Armstrong is co-founder of Ocular Technologies, a tele-ophthalmology device company.

They relay signals from one input down a chain of multiple interconnected neurons that ultimately outputs a conclusion about the initial input (*Figure 1*). Conclusions can include results of disease screening, diagnosis or disease grading and classification.[1]

Retina has an abundance of imaging modalities at our disposal. While fundus photography and fluorescein angiography have been incorporated into clinical practice for years, newer modalities such as optical coherence tomography and OCT angiography have experienced rapid uptake. The prevalence of clinical images, and the ability of these images to directly assess neuronal and vascular tissue, makes retina an ideal field to take advantage of the promise of AI.

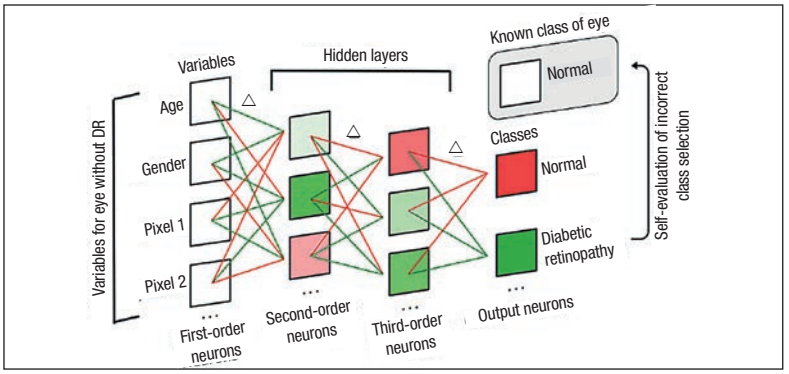

Figure 1. A model neural network model showing incorrect class selection and subsequent weighted connection modifications.[1] A neural network is composed of multiple neuronal layers. The first-order neurons represent clinical variables for an eye without diabetic retinopathy. Weighted connections are represented as positively weighed (green) or negatively weighted (red) lines. The second-order and third-order neurons comprise the hidden layers. The algorithm has output a class selection of "diabetic retinopathy," which is incorrect. The algorithm compares the output of "diabetic retinopathy" to the known class of the eye, "normal." Since the output was incorrect, the algorithm determines which weighted neuronal connections to modify (indicated by △). (*Used with permission of Wolters Kluwer Health*)

AI in disease detection

The prevalence of age-related and comorbid ophthalmic conditions is rising as the population ages. Worldwide, the number of people with diabetes is estimated to increase from 415 million today to 642 million by 2040.[2] Each patient with diabetes will require a diabetic eye screening to detect treatable disease, although fewer than half of them are currently screened annually.[3,4]

Age-related macular degeneration is already the leading cause of central vision loss in the United States, and the worldwide prevalence is estimated to rise from 196 million in 2020 to 288 million by 2040.[4] This increase in retinal pathology will drive utilization of ophthalmic care services in the United States and elsewhere, but the number of retina specialists isn't expected to increase commensurately.[5,6] This increased demand for eye care, along with technological advancements in the field of ophthalmology and computer science, has led to a greater focus on AI.

ML algorithms have shown incredible promise in the detection of diseases such as DR and AMD.[7,8] Beyond this, AI algorithms have also shown proficiency in grading disease and properly discriminating patients with mild disease from those with referable disease.[8-10] These technological advances stand to offload screening exams from ophthalmologists to computer-based screening programs, which will require lower-compensated and less-skilled operators. As routine screening exams are increasingly relegated to AI-enabled machines and cameras, patient referrals to practicing retina specialists will inevitably increase with a commensurate escalation in the demand for treatment of vision-threatening disease.

Predicting treatment needs

AI-based algorithms have also demonstrated the ability to predict the need for treatment in various patient populations. For example, algorithms can utilize OCT images to determine which patients with AMD will require anti-VEGF injections.[11] Patients with diabetes also benefit from similar algorithms that can predict who will need laser treatment, anti-VEGF injections or surgery. [12]

Predicting patient outcomes in retinal disease has also been assessed using AI

algorithms. Using OCT images from patients on anti-VEGF therapy for neovascular AMD, multiple studies have found that a patient's future visual acuity can be predicted with relative certainty.[13,14] The ability to prognosticate could help in patient counseling and encouraging medication adherence.

Lastly, retinal imaging has been used to assess nonophthalmic disease indicators and overall patient health. One of the earliest studies to use fundus photography to assess patient health demonstrated an ability to predict a patient's gender, smoking status, systolic blood pressure and other metrics.[15] More recent studies have shown an ability to detect Alzheimer's disease,[16,17] renal function[18] and autism spectrum disorder[19] (*Figure 2*). While the research in these areas is still early, there's vast potential to improve patient care and detect disease early with non-invasive retinal imaging.

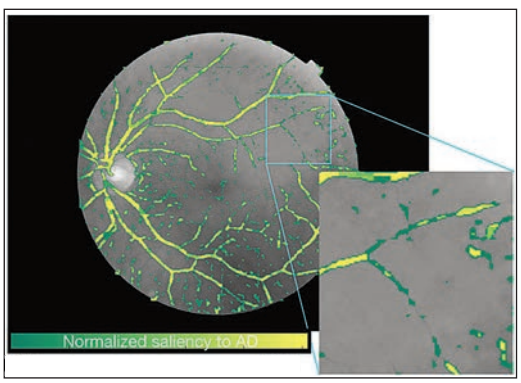

Figure 2. Generated saliency map of a fundus photograph after the use of artificial intelligence for the detection of Alzheimer's disease in a patient.[17] A general observation that researchers can make through the saliency map is that small vessels contribute more than major vessels to Alzheimer's disease classification. Green pixels are more salient for classifying Alzheimer's disease while yellow pixels don't significantly contribute to this classification. According to this saliency map, small vessels and capillary vessels are more important in determining whether this image belongs to an Alzheimer's disease subject. (*Image used under creative commons license. Source: Science Reports*)

Clinical readiness

While the scientific community seems to be publishing results of new and innovative retinal image-based AI algorithms for disease detection, triage and prognostication at a breakneck pace, commercial applications of these technologies is lagging behind. A few standout retinal imaging technologies incorporating AI have undergone FDA approval and are now on the market.

In the United States, IDx-DR (Digital Diagnostics) was the first autonomous AI technology approved for use in detection of pathology without the need for a physician to review the images.[20] Marketed for use in primary-care offices and other non-ophthalmic outpatient settings with patients with diabetes, the technology can autonomously, through the use of a Topcon NW400 fundus camera, differentiate patients with referable DR, defined as moderate DR or macular edema, from those with non-referable DR. Based on the autonomous read of the fundus photograph, the program can recommend that the physician capturing the image refer the patient to an ophthalmologist when appropriate.

Retina specialists will probably not purchase this AI tool for use in their own offices, but its implementation in integrated health systems or local referral networks stands to increase both the number of patients with DR referred to retina specialists and the percentage of patient referrals with pathologic findings requiring treatment.

This autonomous system allows patients with diabetes to obtain ophthalmic care without the need to visit an ophthalmologist and thus improve access to care, while increasing the proportion of a primary-care physician's patient panel that achieves the quality metric of obtaining an annual diabetic screening exam. The cost of the IDx-DR system, which includes the software and the Topcon camera, may be prohibitive for small primary-care practices, but bigger practices caring for a large proportion of patients with diabetes could achieve cost-effectiveness.

Recently, a second autonomous AI screening technology for DR was approved, EyeArt (Eyenuk). While the EyeArt program can detect more-than-mild DR similar to IDx-DR, it also boasts the ability to detect vision-threatening DR. The system performed remarkably well, with the company reporting a sensitivity of 96 percent and specificity of 88 percent in detecting referable DR, and sensitivity of 92 percent and specificity of 94 percent for detecting vision threatening DR.[21] Real-world trials of the technology have found similar accuracy in detecting DR.[22] Similar to IDx-DR, this

technology is beneficial for patients with diabetes in primary-care practices.

AI technology on the horizon

Additional AI-based technologies are being evaluated that could significantly influence the future of retina practice. Notal Vision is developing a home-based OCT diagnostic device intended to be used by patients with nAMD. While this device is not yet FDA approved, it's in clinical trials and stands to improve remote patient monitoring and earlier detection of pathologic changes for patients with AMD, thus enabling retina specialists to treat disease earlier in its course and intervene before significant fibrosis and permanent vision loss occurs.

Additional products are undoubtedly in the pipeline, including a result of a recently announced collaboration between Novartis Pharma AG and RetinAI in assessing disease severity in patients with neovascular AMD.[23]

Clinical workflow

Today the only retina-based AI technologies approved by the FDA are devoted to DR screening. Incorporating these novel technologies into existing workflows requires a coordinated effort between retina specialists and non-retina providers caring for patients with diabetic disease.[24] If the technology is to be successful, it should be implemented in patient populations and care sites with a high prevalence of diabetes. Personnel will need to be tasked with identification of patients with diabetes and coordination of fundus photography images.

Because high-quality fundus photographs are required for the AI to operate effectively, staff will need training in proper operation of the fundus camera and should maintain their skills by using the camera frequently.

Once the images are captured and the report generated, patient education on the findings is necessary to encourage proper follow-up with a retina specialist. Coordinated referral placement should ensure ease of access for patients.

Privacy and regulation considerations with AI

While artificial intelligence-based systems currently on the market don't transmit protected health information or clinical images off-site to enable the algorithm to detect evidence of diabetic retinopathy, physicians should be mindful that future AI technologies may not operate similarly.

Clinical images of the retina should be stored securely and, when desired, should be transmitted between providers securely. Protection of patient privacy is paramount, and data security violations can result in significant fines or litigation.

State regulations require that physicians providing patient care be licensed to practice medicine within that jurisdiction. Lastly, antikickback statues prohibit physicians from referring patients to entities with which they have a financial relationship. This can complicate referral relationships if a retina practice provides an AI-based technology to the referring clinician and is subsequently sent patients.

The complexity of these issues make it prudent to seek professional counsel before you implement AI-based technologies and screening programs.

Financial sustainability of any DR screening program, including those using AI-based technologies, requires careful consideration of billing and reimbursement. Fortunately, a novel CPT code, 9225X, has been created to accommodate AI-based retinal screening platform utilization.[25]

As increasingly varied AI-based retinal technologies enter the market, physicians will need to make similar considerations and carefully incorporate the tools into existing workflows. There will be no one-size-fits-all approach. Due to cost considerations, varying prevalence of diseases in target populations and heterogenous clinical practice patterns, different health-care systems and physicians will need to implement the technologies differently.

Bottom line

AI has entered the mainstream and is ready to be incorporated into retina referral networks. Current FDA-approved, AI-based devices are meant to screen for referable DR and vision threatening DR in primary-care clinics, but products on the horizon will go well beyond DR screening and could be integrated into retina practices, be used by referring providers, or provide remote monitoring in patients' homes.

Ongoing research shows promising results in retinal and systemic disease detection,

(Continued on page 37)

Five evidence-based answers for PVD, retinal breaks

Answers to commonly encountered clinical questions about the clinical course of posterior vitreous detachment and symptomatic retinal breaks.

Jonathan F. Russell, MD, PhD

William E. Smiddy, MD

Harry W. Flynn Jr. MD

By Jonathan F. Russell, MD, PhD, William E. Smiddy, MD, and Harry W. Flynn Jr., MD

Take-home points

- Patients presenting with acute, symptomatic posterior vitreous detachment have a high likelihood of retinal breaks.
- Rhegmatogenous retinal detachment occurs in a significant percentage of patients with untreated symptomatic horseshoe retinal tears.
- After treatment of a symptomatic retinal break, it's not uncommon for additional breaks to occur.
- Fellow eyes often have retinal breaks or RRD during long-term follow-up.

Retinal breaks are full-thickness discontinuities in the neurosensory retina. Asymptomatic retinal breaks have a very low risk of retinal detachment.[1] Retinal breaks associated with symptoms of floaters and/or photopsias occurring in the setting of acute posterior vitreous detachment are more likely to cause rhegmatogenous retinal detachment.

Here, we answer five commonly encountered clinical questions about the course of PVD and symptomatic retinal breaks that should be considered in formulating management decisions.

1 How often is symptomatic PVD associated with a retinal break?

A retinal break is present in up to 16 percent of acute, symptomatic PVDs (*Table 1*).[2-5] If no retinal break appears upon presentation of acute, symptomatic PVD, there's a 2 percent rate of a retinal break in the subsequent weeks.[1]

A Weiss ring, defined as peripapillary glial tissue suspended in the vitreous cortex, is present in about half of symptomatic PVDs with an associated retinal break.[6] The likelihood of finding a retinal break is increased in the presence of a Shafer's sign (90 percent)[7,8] and/or vitreous hemorrhage (50 to 70 percent) (*Figure 1*).[2,3]

Other risk factors for retinal breaks include myopia, aphakia, pseudophakia, cataract surgery, lattice retinal degeneration, uveitis, retinitis, hereditary vitreoretinopathies and trauma.

Table 1. Prevalence of retinal breaks in symptomatic posterior vitreous detachment

No. of eyes	Retinal break (%)	References
84	11	Jaffe 1968[2]
150	46	Kanski, Daniel 1975[18]
172	8	Novak, Welch 1984[26]
350	14	Byer 1994[3]
189	11	Dayan, et al. 1996[24]
219	8.2	Coffee, et al. 2007[25]
7,999	16	Uhr, et al. 2020[4]

Bios

Dr. Russell is chief resident and director of ocular trauma at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine.

Dr. Smiddy and Dr. Flynn are professors of ophthalmology at Bascom Palmer Eye Institute.

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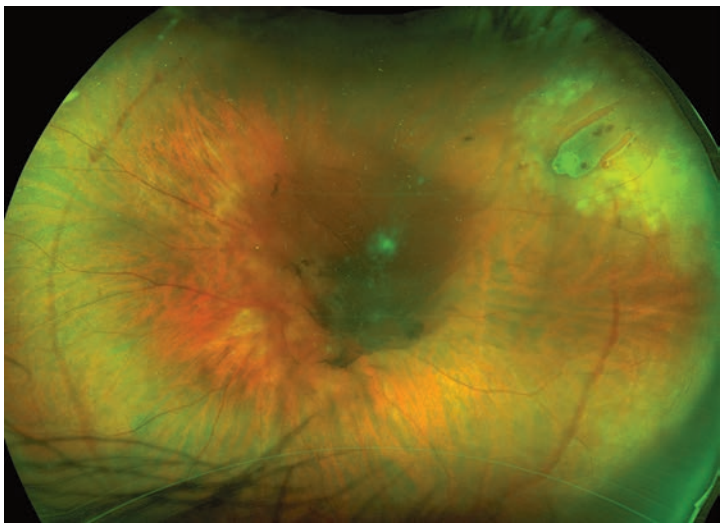

Figure 1. Symptomatic posterior vitreous detachment with retinal break. There is a central area of vitreous hemorrhage and peripheral hemorrhage that demarcate the circumferential extent of PVD. The break has a cuff of subretinal fluid. Laser photocoagulation burns barricade the break to the ora serrata. Visual acuity was 20/400.

2 How often do symptomatic retinal breaks lead to RD without treatment?

Untreated, symptomatic horseshoe tears are reported to lead to RD in 30 to 50 percent of cases (*Table 2*).[9,10] Retinal break features that are particularly high risk for progression to RD include breaks of acute onset, superior location, large size and surrounding subretinal fluid.

Some breaks are associated with subclinical RD, which is defined as an extension of subretinal fluid at least 1 disc diameter away from the break but not more than 2 disc diameters posterior to the equator. Operculated retinal breaks have a low risk of progression to RD because the operculum represents relief of the vitreoretinal traction.

Table 2. Progression to detachment in untreated symptomatic retinal breaks

No. of eyes	Progression to retinal detachment (%)	References
16	38	Colyear, Pischel 1956[8]
31	36	Davis 1974[9]
21	47	Shea et al. 1974[29]
50	28	Byer 1994[28]

3 How often do subsequent retinal breaks occur after treatment of the first break?

Acute-onset, symptomatic horseshoe tears are generally treated in an effort to reduce the risk of progression to RD. Retinal breaks are treated with retinopexy by cryotherapy or laser photocoagulation. If severe media opacity prohibits either procedure, vitrectomy may be necessary.

Subsequent retinal breaks occur after treatment of the first retinal break in 5 to 14 percent of eyes (*Table 3*). About half of subsequent breaks occur within four to six

Table 3. Subsequent retinal breaks and retinal detachment after retinopexy for retinal breaks

No. of eyes	New break (%)	RRD (%)	ERM (%)	References
301	5.5	6	1	Robertson, Norton 1973[14]
177	7.3	4.5	2	Combs, Welch 1982[15]
74	7.3	2.7	NR	Straatsma, et al 1965[16]
231	NR	5	NR	Chignell, Shilling 1973[17]
701	8	4.7	NR	Kanski, Daniel 1975[18]
231	0	0	0	Morse, Scheie 1974[19]
83	10	NR	NR	Goldberg, Boyer 1980[20]
171	14	9	5	Smiddy, et al. 1991[21]
155	12.2	3	NR	Sharma, et al. 2004[22]
401	10	6	NR	Garoon, et al. 2018[23]
TOTALS				
2,525	**7.9**	**4.8**	**1.7**	

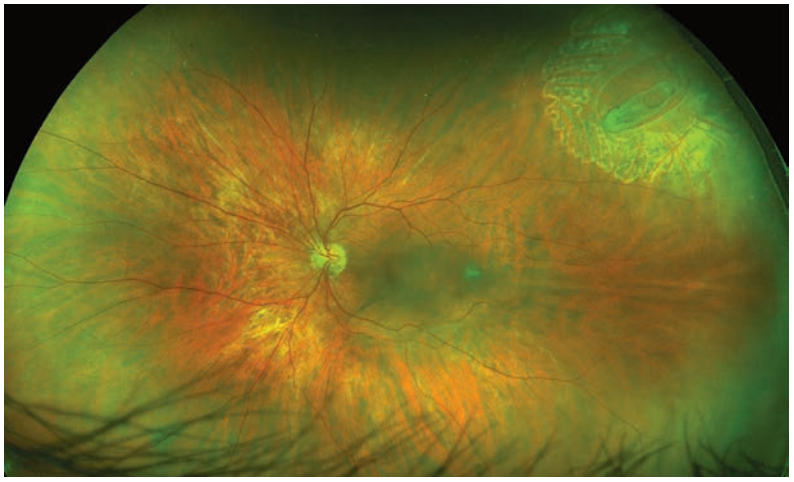

Figure 2. Three months after retinopexy, no retinal detachment and no new retinal breaks have occurred, and the vitreous hemorrhage has resolved. Visual acuity is 20/20.

weeks, but new breaks may occur months or even years later.[5]

4 How often do symptomatic retinal breaks lead to RD despite treatment?

RD occurs in about 5 percent of eyes with symptomatic retinal breaks despite retinopexy (*Table 3, page 35*). This can occur because of inadequate treatment to all margins of the break, if subretinal fluid accumulates before chorioretinal adhesion from retinopexy is complete, or because of missed or new breaks. Only about one-third of RDs occur within six weeks of treatment.[5]

5 How often do retinal breaks and RD occur in the fellow eye?

Fellow eyes in RD have an 8.4 percent rate of retinal breaks and a 14.5 percent rate of lattice retinal degeneration at presentation.[11] The risk of RD in the fellow eye is 7 to 23 percent; 1 to 2 percent of eyes present with simultaneous bilateral RD.[11,12]

Prophylactic treatment of lattice degeneration in fellow eyes may reduce the risk of RD two- or threefold,[13] although this has been debated because new retinal breaks often develop in untreated areas or may occur at the edge of retinopexy scars if a PVD occurs or extends.[14]

Management of symptomatic PVD

While there are no prospective, randomized controlled trials to guide management, it's generally accepted that acute, symptomatic PVD merits evaluation with thorough ophthalmoscopy that usually includes scleral depression. If media opacity precludes complete ophthalmoscopy to the ora serrata, B-scan ultrasonography and frequent clinical reexamination are alternatives.

The risk of progression of asymptomatic breaks, even when horseshoe-shaped, to RD is exceedingly low, so they can generally be observed. However, acute and symptomatic horseshoe tears should be treated with retinopexy (*Figure 2*).

Retinopexy can be performed with either laser photocoagulation or cryotherapy. Retinopexy should encompass the entire margin of the retinal break and any associated lattice retinal degeneration. If this isn't possible, retinopexy burns should surround the break extending to the ora serrata.

Giant retinal tears are generally treated with surgery. RD is usually treated with surgery, which may include pneumatic retinopexy, pars plana vitrectomy, scleral buckle or a combination of scleral buckle and vitrectomy.

Regardless of whether or not a patient presents with a retinal break and receives treatment, the potential for subsequent breaks or RD warrants longitudinal follow-up when possible. Detailed guidelines for follow-up have been published.[1] Patients should also be clearly counseled that they need prompt reevaluation if they develop new symptoms of photopsias, floaters or visual field deficits—as opposed to persistence of existing symptoms.

Bottom line

Retinal breaks are a common, vision-threatening occurrence. Early recog-

nition and treatment of acute, symptomatic retinal breaks will reduce rates of RRD and subsequent vision loss. Additional breaks can occur after treatment of the initial break and fellow eyes may also have similar events. Regular follow-up is indicated.

REFERENCES

1. Posterior vitreous detachment, retinal breaks, and lattice degeneration PPP – 2019. American Academy of Ophthalmology. Updated October 2019. https://www.aao.org/preferred-practice-pattern/posterior-vitreous-detachment-retinal-breaks-latti Accessed March 4, 2021.
2. Jaffe NS. Complications of acute posterior vitreous detachment. Arch Ophthalmol. 1968;79:568-571
3. Byer NE. Natural history of posterior vitreous detachment with early management as the premier line of defense against retinal detachment. Ophthalmology. 1994;101:1503-1513.
4. Uhr JH, Obeid A, Wibbelsman TD, et al. Delayed retinal breaks and detachments after acute posterior vitreous detachment. Ophthalmology. 2020;127:516-522.
5. Goh YW, Ehrlich R, Stewart J, et al. The incidence of retinal breaks in the presenting and fellow eyes in patients with acute symptomatic posterior vitreous detachment and their associated risk factors. Asia Pac J Ophthalmol (Phila.) 2015;4:5-8.6. Brod RD, Lightman DA, Packer AJ, et al. Correlation between vitreous pigment granules and retinal breaks in eyes with acute posterior vitreous detachment. Ophthalmology. 1991;98:1366-1369.
7. Tanner V, Harle D, Tan J, et al. Acute posterior vitreous detachment: The predictive value of vitreous pigment and symptomatology. Br J Ophthalmol. 2000;84:1264-1268.
8. Colyear BH Jr, Pischel DK. Clinical tears in the retina without detachment. Am J Ophthalmol. 1956;41:773-792.
9. Davis MD. Natural history of retinal breaks without detachment. Arch Ophthalmol. 1974;92:183-194.
10. Mitry D, Singh J, Yorston D, et al. The fellow eye in retinal detachment: Findings from the Scottish Retinal Detachment study. Br J Ophthalmol. 2012;96:110-113.
11. Gonzales CR, Gupta A, Schwartz SD, et al. The fellow eye of patients with rhegmatogenous retinal detachment. Ophthalmology. 2004;111:518-521.
12. Folk JC, Arrindell EL, Klugman MR. The fellow eye of patients with phakic lattice retinal detachment. Ophthalmology. 1989;96:72-79.
13. Chauhan DS, Downie JA, Eckstein M, et al. Failure of prophylactic retinopexy in fellow eyes without a posterior vitreous detachment. Arch Ophthalmol. 2006;124:968-971.
14. Robertson DM, Norton EW. Long-term follow-up of treated retinal breaks. Am J Ophthalmol. 1973;75:395-404.
15. Combs JL, Welch RB. Retinal breaks without detachment: Natural history, management and long term follow-up. Trans Am Ophthalmol Soc. 1982;80:64-97.
16. Straatsma BR, Allen RA, Christensen RE. The prophylaxis of retinal detachment. Trans Pac Coast Oto-Ophthalmol Soc Ann Meet. 1965;46:211-236.
17. Chignell AH, Shilling J. Prophylaxis of retinal detachment. Br J Ophthalmol. 1973;57:291-298.
18. Kanski JJ, Daniel R. Prophylaxis of retinal detachment. Am J Ophthalmol. 1975;79:197-205.
19. Morse PH, Scheie HG. Prophylactic cryoretinopexy of retinal breaks. Arch Ophthalmol. 1974;92:204-207.
20. Goldberg RE, Boyer DS. Sequential retinal breaks following a spontaneous initial retinal break. Ophthalmology. 1980;88:10-12.
21. Smiddy WE, Flynn HW Jr, Nicholson DH, et al. Results and complications in treated retinal breaks. Am J Ophthalmol. 1991;112:623-631.
22. Sharma MC, Regillo CD, Shuler MF, et al. Determination of the incidence and clinical characteristics of subsequent retinal tears following treatment of the acute posterior vitreous detachment-related initial retinal tears. Am J Ophthalmol. 2004;138:280-284.
23. Garoon RB, Smiddy WE, Flynn HW Jr. Treated retinal breaks: Clinical course and outcomes. Graefes Arch Clin Exp Ophthalmol. 2018;256:1053-1057.
24. Dayan MR, Jayamanne DG, Andrews RM, et al. Flashes and floaters as predictors of vitreoretinal pathology: Is follow-up necessary for posterior vitreous detachment? Eye. 1996;10:456-458.
25. Coffee RE, Westfall AC, Davis GH, et al. Symptomatic posterior vitreous detachment and the incidence of delayed retinal breaks: Case series and meta-analysis. Am J Ophthalmol. 2007;144:409-413.
26. Novak MA, Welch RB. Complications of acute symptomatic posterior vitreous detachment. Am J Ophthalmol. 1984;97:308-314.
27. Kanski JJ. Complications of acute posterior vitreous detachment. Am J Ophthalmol. 1975;80:44-46.
28. Byer NE. Natural history of posterior vitreous detachment with early management as the premier line of defense against retinal detachment. Ophthalmology. 1994;150:1504-1513.
29. Shea M, Davis MD, Kamel I. Retinal breaks without detachment, treated and untreated. Mod Probl Ophthalmol.1974;12:97-102.

AI in retina: Ready for prime time?

(Continued from page 33)

grading and prognostication. In time, these AI algorithms will enter clinical practice and fulfill the potential of AI-based retinal imaging in advancing patient care.

REFERENCES

1. Armstrong GW, Lorch AC. A(eye): A Review of current applications of artificial intelligence and machine learning in ophthalmology. Int Ophthalmol Clin. 2020;60:57-71.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40-50.
3. Murchison AP, Hark L, Pizzi LT, et al. Non-adherence to eye care in people with diabetes. BMJ Open Diabetes Res Care. 2017;5:e000333.
4. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. Lancet Glob Health. 2014;2:e106-e116.
5. Feng PW, Ahluwalia A, Feng H, Adelman RA. National trends in the United States eye care workforce from 1995 to 2017. Am J Ophthalmol. 2020;218:128-135.
6. Gibson DM. The local availability of eye care providers and the vision health of adults in the United States. Ophthalmic Epidemiol. 2016;23:223-231.
7. Kermany DS, Goldbaum M, Cai W, et al. Identifying medical diagnoses and treatable diseases by image-based deep learning. Cell. 2018;172:1122-1131.e9.
8. Ting DSW, Cheung CY, Lim G, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. JAMA. 2017;318:2211-2223.
9. Burlina P, Pacheco KD, Joshi N, Freund DE, Bressler NM. Comparing humans and deep learning performance for grading AMD: A study in using universal deep features and transfer learning for automated AMD analysis. Comput Biol Med. 2017;82:80-86.
10. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA. 2016;316:2402-2410.
11. Prahs P, Märker D, Mayer C, Helbig H. Deep Learning zur Unterstützung der Therapieentscheidung bei intravitrealen Injektionen [Deep learning to support therapy decisions for intravitreal injections]. Ophthalmologe. 2018;115:722-727.
12. Takahashi H, Tampo H, Arai Y, Inoue Y, Kawashima H. Applying artificial intelligence to disease staging: Deep learning for improved staging of diabetic retinopathy. PLoS One. 2017;12:e0179790.
13. Aslam TM, Zaki HR, Mahmood S, et al. Use of a neural net to model the impact of optical coherence tomography abnormalities on vision in age-related macular degeneration. Am J Ophthalmol. 2018;185:94-100.
14. Schmidt-Erfurth U, Bogunovic H, Sadeghipour A, et al. machine learning to analyze the prognostic value of current imaging biomarkers in neovascular age-related macular degeneration. Ophthalmol Retina. 2018;2:24-30.
15. Poplin R, Varadarajan AV, Blumer K, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng. 2018;2:158-164.
16. Lemmens S, Van Craenendonck T, Van Eijgen J, et al. Combination of snapshot hyperspectral retinal imaging and optical coherence tomography to identify Alzheimer's disease patients. Alzheimers Res Ther. 2020;12:144.
17. Tian J, Smith G, Guo H, et al. Modular machine learning for Alzheimer's disease classification from retinal vasculature. Sci Rep. 2021;11:238.
18. Sabanayagam C, Xu D, Ting DSW, et al. A deep learning algorithm to detect chronic kidney disease from retinal photographs in community-based populations. Lancet Digit Health. 2020;2:e295-e302.
19. Lai M, Lee J, Chiu S, et al. A machine learning approach for retinal images analysis as an objective screening method for children with autism spectrum disorder. E Clin Med. 2020;28:100588.
20. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digit Med. 2018;1:39.
21. Lim J, Bhaskaranand M, Ramachandra C, Bhat S, Solanki K, Sadda S. Artificial intelligence screening for diabetic retinopathy: analysis from a pivotal multi-center prospective clinical trial. Paper presented at: ARVO Imaging in the Eye Conference; April 27, 2019; Vancouver, BC, Canada.
22. Bhaskaranand M, Ramachandra C, Bhat S, et al. The value of automated diabetic retinopathy screening with the EyeArt system: A study of more than 100,000 consecutive encounters from people with diabetes. Diabetes Technol Ther. 2019;21:635-643.
23. RetinAI announces collaboration with Novartis to provide artificial intelligence solutions in ophthalmology [press release]. RetinAI, Bern, Switzerland. December 8, 2020. https://www.retinai.com/press-releases Accessed February 12, 2021.
24. Horton MB, Brady CJ, Cavallerano J, et al. Practice guidelines for ocular telehealth-diabetic retinopathy, third edition. Telemed J E Health. 2020;26:495-543.
25. American Medical Association. CPT Editorial Summary of Panel Actions May 2019. August 26, 2019. https://www.ama-assn.org/system/files/2019-08/may-2019-summary-panel-actions.pdf Accessed February 12, 2021.

Confronting the cyberbully

Some guidance for retina specialists and physicians when they're attacked on social media.

By David R.P. Almeida, MD, MBA, PhD

David R.P. Almeida, MD, MBA, PhD

Previously I covered how retina specialists can combat false claims on social media with strategies to mitigate misinformation, disinformation and propaganda. Unfortunately, doing so may lead to physicians being attacked for their social media statements.

Physicians are not spared

A recently published research letter in *JAMA Internal Medicine* states that one in four physicians who use social media reported being personally cyberbullied, and one in six women physicians faced the additional threat of being sexually harassed online.[1] It's worth noting that this study was performed prior to the COVID-19 pandemic, and this has significant implications for physicians on social media today.

Cyberbullying refers to a disparate number of online methods used to intimidate others. This may vary in scope and severity from online trolling (e.g., disinformation or propaganda comments in reply to a physician post), anonymous calls to practice or hospital leadership "reporting" the physician's online statements, or doxxing—defined as violation of privacy by having your personal information published online.[2] A complicating factor is that the three characteristics that define bullying—intent, repetition and power imbalance—don't always translate directly in digital behaviors.[3]

Like a punch in the mouth

Cyberbully attacks are unfortunate and unwarranted responses to what I believe is your genuine online voice aimed at promoting health. However, these bruises, blisters and burns will need to be negotiated within the rocky evolving landscape of social media.

So, given the likelihood of cyberbully insults, what is your best strategy to counter? Boxer Mike Tyson once said, "Everyone has a plan until they get punched in the mouth." What happens when you and your online voice get punched in the mouth?

Maintain your integrity

Foremost, realize and accept that you will eventually get cyberbullied or trolled online. When it does happen, be composed and don't be rattled, but be committed to your message. No shame in taking a punch, especially if your counterattack is poised and positioned. There's courage and power in vulnerability so don't waste this opportunity to emphasize your communication.

Second, be deliberate in your response and maintain the integrity of your online brand. As a retina specialist and physician, your social media voice can be a tremendous asset to the online advocacy of a position you feel strongly about. Whether it's discussing myths concerning a given treatment or speaking out on social justice, your Twitter posts or website comments can be victories when they empower patients, colleagues or the public at large.

Strength in numbers

Finally, if you find the cyberbullying incessant, look for strength in numbers. Groups like #medtwitter (www.twitter.com/hashtag/MedTwitter) are examples that, collectively, we have a louder online voice than as isolated individuals.

Not only do these groups offer support to individual members; they offer insights and solutions to online conflicts that likely have happened to other physicians.

Bio

Dr. Almeida is a vitreoretinal surgeon at Erie Retinal Surgery in Erie, Pa.

DISCLOSURE: Dr. Almeida reports no relevant financial relationships.

- Twitter: @davidalmeidamd
- Email: drpa@pm.me.

REFERENCES

1. Pendergrast TR, Jain S, Trueger NS, Gottlieb M, Woitowich NC, Arora VM. Prevalence of personal attacks and sexual harassment of physicians on social media. JAMA Intern Med. Published online January 4, 2021. doi: 10.1001/jamainternmed.2020.7235.
2. Arora V, Pendergrast T, Jain S. Doctors on social media are being cyberbullied and sexually harassed. It's time to change that. Stat. Posted January 5, 2021. https://www.statnews.com/2021/01/05/doctors-on-social-media-are-being-cyberbullied-and-sexually-harassed-its-time-to-change-that/ Accessed February 5, 2021.
3. Englander E, Donnerstein E, Kowalski R, Lin CA, Parti K. Defining cyberbullying. Pediatrics. 2017;140(Suppl 2):S148-S151.

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New E/M codes are here. Now what?

A strategy for meeting the new requirements for Evaluation and Management codes.

By Ellen R. Adams, MBA

While we were struggling to cope with the pandemic, the American Medical Association continued to work toward finalizing the revisions to the Evaluation and Management (E/M) codes.

When we learned what the new documentation requirements entailed, most of us were relieved. It was refreshing to see the elimination of history and exam box checking that had been required to meet the E/M documentation rules.

By now, hopefully, you've learned how to code an E/M service based on medical decision-making—or, less commonly, time. It was a challenging but not overwhelming task to grasp E/M 2021. Presumably you now have a working understanding of the E/M requirements.

Where we've been

Have you figured out what to do with that knowledge? How will you document and code to mitigate fee schedule changes? Do you need to rethink the history and exam you document? Historically, ophthalmologists coded new patient exams with the colloquially named "eye codes" 57 percent of the time, and established patient exams with eye codes nearly 78 percent of the time.[1]

The reason for this coding pattern was because comprehensive eye (920x4) and intermediate eye (920x2) documentation requirements closely match an ophthalmology exam, and traditionally reimbursement for eye codes has been reasonable.

We (reluctantly) used E/M codes to fill a vital role in ophthalmology despite the advantages of eye codes. In particular, the new patient level 4 (99204) and level 5 (99205) codes have a higher reimbursement and were often appropriate for surgical evaluations and very complex cases. The established patient level 3 (99213) code filled a key role for chronic, stable patient exams.

We know where we've been. How have the fee schedule and new documentation guidelines changed recommended coding patterns? To learn the answer, we must first review the 2021 physician fee schedule payment rates.

Where we're going

Fortunately, the proposed rates for eye codes, originally slated to suffer significant cuts, were saved from the chopping block. The final national payment rates from the Centers for Medicare and Medicaid Services showed a slight increase for eye codes and some increases for E/M codes (*Table*).

As you can see from the 2021 rates, payment for new patient exams follows the scale most of us are familiar with: new patient E/M level 4 and 5 (99204 and 99205) pay higher than comprehensive eye (92004). It's important to also note that E/M new patient level 3 (99203) reimburses higher than new intermediate eye (92002). On the established side, comprehensive eye (92014) reimburses close to E/M level 4 (99214), while E/M level 3 (99213) pays about the same as intermediate eye (92012).

Planning your coding strategy

Having the documentation requirements and reimbursement rates in hand, you can plan your strategy for coding exams. Importantly, the lessened E/M documentation requirements offer an opportunity for you and your technician team to do an exam that's relevant, clear and concise while eliminating redundant, excessive and otherwise useless but time-consuming documentation from the chart.

Another consideration is that the eye code documentation requirements persist, so you want to be sure your team captures exam elements required for the eye codes when you use them. With simpler documentation requirements for E/M, there may be capac-

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

Bio
Ms. Adams is a consultant with Corcoran Consulting Group. She can be reached at 1-800-399-6565 or at www.corcoranccg.com.

ity to add one or two patients per clinic day if you can use the time you save in documentation.

A deeper dive into specific strategies is next. Kevin Corcoran of our firm recently performed an analysis of various coding patterns.[2] He looked at four new patient coding scenarios:

- The current national code selection patterns of about 57 percent of new patients coded with eye codes.
- Using eye codes exclusively.
- Using E/M exclusively.
- Shifting to a higher utilization of E/M with the same level of service.

Illustrating the conundrum

Although the outcome of the study indicated the highest revenue benefit from using only E/M codes, that strategy is problematic from a practical standpoint. Some insurance companies prefer eye codes; some E/M exams, especially in retina, won't meet the criteria for reasonable reimbursement. A few examples help illustrate this conundrum.

- ***Example 1.*** A new patient is referred for an eye exam due to longstanding diabetes. A comprehensive exam and optical coherence tomography show the patient has background diabetic retinopathy without macular edema. Treatment includes counseling regarding blood-sugar control. The appropriate E/M code for this exam is 99203; the eye code is 92004.
- ***Example 2***. An established patient comes in for an annual follow-up exam of dry age-related macular degeneration. A comprehensive exam and OCT are performed. Treatment includes counseling and education regarding the signs of conversion to wet AMD as well as instructions to use an Amsler grid daily. The appropriate E/M code will be 99213; the eye code is 92014.

As you can see, abandoning eye codes may result in some missed opportunities. That being said, Mr. Corcoran noted that if an ophthalmologist shifts from the historic utilization of 57 percent eye codes for new patients to a higher utilization of E/M codes (85 percent), the provider will enjoy an increase in annual revenue of about 6 percent.

However, even if no changes are made in coding patterns and a provider continues to utilize eye codes 57 percent of the time for new patients, the provider will see a slight increase in revenue of about 3 percent due to fee schedule adjustments.

Table. 2021 Medicare national physician payment rates[3]

Procedure	New patient		Established patient	
	CPT	National Medicare Rate	CPT	National Medicare Rate
Comprehensive eye	92004	$152	92014	$128
Intermediate eye	92002	$88	92012	$91
Level 5	99205	$224	99215	$183
Level 4	99204	$170	99214	$131
Level 3	99203	$114	99213	$92
Level 2	99202	$74	99212	$57

Crafting your own strategy

Your own strategy should take into account your ability to document an exam appropriately for the level of service you bill, as well as your overall understanding of the new E/M code requirements. And even if you make no changes in your exam code utilization, you should be sure you're capturing the required elements for the exams you submit with eye codes.

To assume you can use the E/M documentation rules for exams for which eye codes are used would be a significant problem. As with all aspects of correct coding, understanding the documentation rules will allow you to code confidently and with the most favorable economic outcome. RS

Your own strategy should take into account your ability to document an exam appropriately for the level of service you bill, as well as your overall understanding of the new E/M code requirements.

REFERENCES

1. Centers for Medicare & Medicaid Services. Physician and other supplier data CY 2018. https://www.cms.gov/research-statistics-data-systems/medicare-provider-utilization-and-payment-data/medicare-provider-utilization-and-payment-data-physician-and-other-supplier/physician-and-other-supplier-data-cy-2018. Updated December 3, 2020. Accessed March 11, 2021.
2. Corcoran KJ. Economic Impact of 2021 Changes on Eye Exams. Corcoran Consulting Group. 2021.
3. Centers for Medicare & Medicaid Services. Medicare Physician Fee Schedule, National Rates, 2021. https://www.cms.gov/medicare/physician-fee-schedule/search?Y=0&T=4&HT=1&CT=0&H1=92004&H2=92014&H3=92002&H4=92012&M=5. Updated January 20, 2021. Accessed March 11, 2021.

Targeted approach to pan-VEGF inhibition

A suprachoroidal formulation of axitinib, approved for renal cell carcinoma, may have potential for treating neovascular AMD.

By Richard Mark Kirkner, Editor

CLS-AX delivered to the suprachoroidal space has the potential as a durable therapy for nAMD. It has demonstrated levels 11 times higher in affected tissues than intravitreal injection.

Axitinib is a tyrosine kinase inhibitor that's been widely used to treat advanced renal cell carcinoma. Like other cancer drugs that have been adapted to treat exudative retinal disease, axitinib targets vascular endothelial growth factor. It has been shown to inhibit three VEGF receptors: VEGFR-1, VEGFR-2 and VEGFR-3.[1]

For renal cell carcinoma, axitinib is marketed as the oral agent Inlyta (Pfizer). Clearside Biomedical is now investigating the efficacy of an injectable suspension of axitinib for treatment in neovascular age-related macular degeneration using its proprietary suprachoroidal microinjector platform. CLS-AX has just completed dosing in the first cohort of OASIS, the ongoing Phase I/IIa clinical trial (NCT04626128).

Allen Hu, MD, a vitreoretinal specialist at Cumberland Valley Retina Consultants in western Maryland and southcentral Pennsylvania and a paid investigator for the OASIS trial, answers questions about CLS-AX.

Q Describe the mechanism of action of axitinib and its potential for the retina.

A Axitinib inhibits corneal, retinal and choroidal angiogenesis in animal models 3-7 by inhibiting VEGFR-1, VEGFR-2 and VEGFR-3. Current AMD therapies focus primarily on VEGF-A blockade and not the VEGF receptors, which may upregulate other forms of VEGF.

Q What are the potential advantages for suprachoroidal administration?

A CLS-AX delivered to the suprachoroidal space has the potential as a durable therapy for nAMD. It has demonstrated levels 11 times higher in affected tissues than intravitreal injection.

Another advantage of suprachoroidal injection is the compartmentalized delivery away from unaffected tissues, minimizing vitreous floaters, the snow globe effect and corneal and anterior segment exposure.

In terms of pharmacokinetics, multiple animal models have shown prolonged duration, demonstrated by the elevated and sustained concentration of axitinib above the half-maximal inhibitory concentration (IC50) in posterior ocular tissues.

Q What's the protocol being used in the OASIS trial?

A OASIS is a Phase I/IIa dose-escalation study to evaluate the safety and tolerability of suprachoroidally delivered axitinib over 12 weeks following an initial aflibercept injection to standardize patients to at least one dose of anti-VEGF therapy. That also allows for an extra visit to further standardize the assessment of vision and anatomic parameters. The study will consist of three planned cohorts with five subjects each.

Q What's been learned from TKIs in other indications that may apply in nAMD?

A Axitinib inhibits VEGF receptors broadly, along with other receptors. Animal studies have shown that axitinib effectively inhibits retinal and choroidal angiogenesis in multiple preclinical models and has better biocompatibility with ocular cells than other TKIs.[2]

Preclinical and clinical studies have shown that broad VEGF inhibition is more promising than focused VEGF-A inhibition.[2] Another preclinical study of several TKIs in wet AMD has shown that axitinib more potently inhibits neovascularization than sunitinib or sorafenib.[3] RS

REFERENCES

1. Prescribing information Inlyta-axitinib, Pfizer. http://labeling.pfizer.com/ShowLabeling.aspx?id=759. Accessed March 11, 2021.
2. Giddabasappa A, Lalwani K, Norberg R, et al. Axitinib inhibits retinal and choroidal neovascularization in in vitro and in vivo models. Exp Eye Res. 2016;145:373-379.
3. Yuan X, Shin CS, Isenhart SC, Pflugfelder SC, Acharya G. Ocular drug delivery nanowafer with enhanced therapeutic efficacy. ACS Nano. 2015;9:1749-1758.

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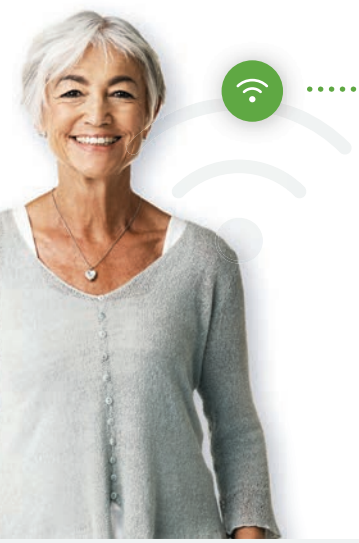

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References: 1. Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina.* 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

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