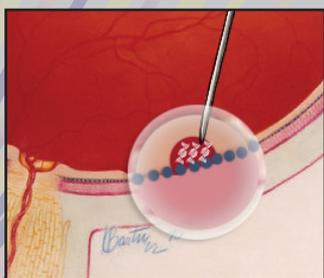


# RETINA SPECIALIST

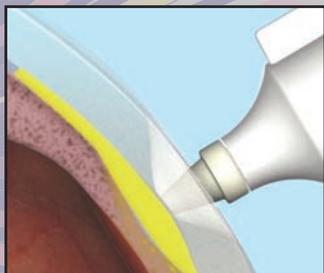
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# EYLEA<sup>®</sup>

## (aflibercept) Injection

### For Intravitreal Injection



#### INDICATIONS AND IMPORTANT SAFETY INFORMATION

##### INDICATIONS

EYLEA<sup>®</sup> (aflibercept) Injection 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) in patients with DME.

##### CONTRAINDICATIONS

- EYLEA<sup>®</sup> (aflibercept) Injection 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.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

**REGENERON**

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# START WITH EYLEA.

AS DEMONSTRATED IN PHASE 3 CLINICAL TRIALS

## START WITH EYLEA.

For approved indications, EYLEA offers flexibility across patient types and dosing options.<sup>1</sup>

LEARN MORE ABOUT ROBUST FIRST-LINE DATA AT [HCP.EYLEA.US](http://HCP.EYLEA.US)

- 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.

*Please see Brief Summary on following pages.*

**Reference: 1.** EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2018.

## 1 INDICATIONS AND USAGE

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

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

## 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 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 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**

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

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

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

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

Adverse Reactions	CRVO		BRVO	
	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).** 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**

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	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.

## 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 in 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.  
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Tarrytown, NY 10591

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Issue Date: November 2018  
Initial U.S. Approval: 2011

Based on the August 2018  
EYLEA® (aflibercept) Injection full  
Prescribing Information.

US-LEA-13708(2)a

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Jobson Medical Information



# In search of a better mousetrap

“Build a better mousetrap, and the world will beat a path to your door.” This metaphor, credited to Ralph Waldo Emerson,<sup>1</sup> embodies the power of innovation. Indeed, mousetraps are the most frequently invented device in U.S. history, with more than 4,400 patents issued since the U.S. Patent Office opened in 1838—and an estimated 10 times that many submissions rejected.

For exudative and inflammatory retinal diseases, current therapeutics are remarkably effective. Yet, thankfully, the ethos of innovation that defines the retina space continues to lead to the development of next-generation mousetraps.

Mark Barakat, MD, discusses suprachoroidal drug delivery and Xipere (Clearside Biomedical), projected to launch commercially in the United States in early 2020 (page 18). Differentiating our toolbox beyond intravitreal and sub-Tenon’s injections, clinicians will, for the first time, have an approved mousetrap to readily access the suprachoroidal space in clinic.

Repeated intravitreal anti-VEGF injections are incredibly safe and effective for the management of neovascular age-related macular degeneration. Nevertheless, efficacy and durability limitations of current anti-VEGF formulations afford ample room for new mousetraps. Arshad Khanani, MD, and colleagues describe the ongoing Phase III trial of the Port Delivery System with

ranibizumab (Genentech) and the underlying Phase II data, which aim to bring a hardware-based surgical solution to the management of nAMD (page 20).

Nicolas Yannuzzi, MD, and Audina Berrocal, MD, describe their experience, both technical and personal, with Luxturna (voretigene neparvovec, Spark Therapeutics), the first FDA-approved gene therapy for a genetic disease (page 22). The tremendous time and resources invested in this vanguard treatment appear poised to usher in an extraordinary wave of new investigational products into clinical trials targeting diseases ranging from the rare to the commonplace, shepherded by companies including Adverum, Clearside, IVERIC Bio, REGENXBIO and Roche, among many others.

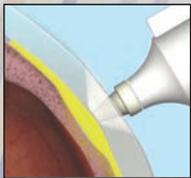
Among thousands of patented mousetraps, fewer than two dozen have made a profit in the marketplace. Newer isn’t always better. The road to commercial viability in retina is cluttered with failed products. Yet, as there remains tremendous opportunity to deliver improved outcomes for our patients, our field of visionaries will certainly continue to refine and innovate in search of the perfect mousetrap. 

#### REFERENCE

1. Hope J. A Better Mousetrap. *American Heritage Magazine*. 1996;47(6). <https://www.americanheritage.com/better-mousetrap>. Accessed May 8, 2019.

## FEATURES

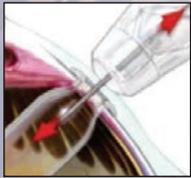
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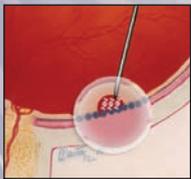
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## Protocol V: Treatments show little difference for DME eyes with $\geq 20/25$ VA

**R**esults from the Diabetic Retinopathy Clinical Research Retina Network's Protocol V study have shown that treatment-naïve patients with good visual acuity but who have center-involved diabetic macular edema can undergo observation and maintain good vision at a rate comparable to patients treated with intravitreal injections or laser photocoagulation, according to results presented at the annual meeting of the Association for Research in Vision and Ophthalmology.<sup>1</sup>

Specifically, the study reported no significant difference in VA loss at two years regardless of whether the patient was treated with intravitreal drugs (16 percent), laser photocoagulation (17 percent) or left to observation (19 percent).

While the percentage of eyes with VA  $\geq 20/20$  was "significantly greater with aflibercept (Eylea, Regeneron Pharmaceuticals) than observation but not laser photocoagulation (one of five secondary visual acuity outcomes at two years and the only significant difference)," the range was such (about 2 letters) that its clinical significance is questionable, the DRCR.net authors wrote in the

article simultaneously posted online by the *Journal of the American Medical Association*.

Protocol V involved patients with center-involved DME and VA  $\geq 20/25$ . Second author Adam R. Glassman, MS, noted at ARVO that "it is a pretty common scenario" to have "a very small percentage" of patients with center-involved DME and good vision (20/25 or 20/32 or better) lose 1 line of vision or more at one year.

In Protocol V, 702 randomized participants completed two-year follow-up. For eyes with VA that decreased from baseline, aflibercept was initiated in 25 and 34 percent of the laser photocoagulation and observation groups, respectively. At two years, the percentage of eyes with a  $\leq 5$ -letter visual acuity decrease was 16 percent, 17 percent and 19 percent in the aflibercept, laser photocoagulation and observation groups, respectively.

The study found no statistically significant differences among groups when looking at  $>10$  letter loss at two years, lead author Carl W. Baker, MD, said. There were no statistical differences in the percentage of eyes that gained vision,

either, but "these eyes had good vision, so there was not a lot of room to gain," Dr. Baker said.

"In Protocol V, the VA of 20/20 or better at two years was 77 percent in the aflibercept group, 71 percent in the laser group and 66 percent in the observation group," he said.

Mr. Glassman noted the strategies for retreatment or treatment were quite different among the arms. "The aflibercept participants came back every four weeks through the first 24 weeks," he said. "After 24 weeks, their visit schedule could extend from anywhere from eight to 16 weeks, depending on their treatment and their clinical course."

The laser and observation participants were seen somewhat less frequently, at least initially. "They had visits at eight weeks and then again at 16 weeks, and we didn't see them after that for another 16 weeks and another 16 weeks thereafter," he said. If optical coherence tomography indicated worsening of center-involved DME, then patients returned earlier for additional visits.

Baseline VA was similar across the arms, with some patients having

### IN BRIEF

The Food and Drug Administration gave final approval to an expanded indication for aflibercept (Eylea, Regeneron Pharmaceuticals): To treat all stages of diabetic retinopathy, with dosing as frequent as every four weeks after the first 20 weeks of treatment.

The FDA has accepted the biological license application for Novartis' highly anticipated brolicizumab, a small-molecule anti-VEGF agent

for treatment of neovascular age-related macular degeneration. If approved, Novartis anticipates launching brolicizumab by the end of the year.

The FDA has lifted a clinical hold on Adverum Biotechnologies' gene therapy candidate ADVM-022 treatment for nAMD. The action allows dose escalation in the second cohort of the OPTIC Phase I trial at a dose three times higher than that in the first cohort. Dosing of the second cohort is expected to begin in June.

20/16 or better, Dr. Baker said. The mean number of visits was “around 18 in the groups that were treated initially with aflibercept,” Dr. Baker said. “In the laser and observation groups, the mean number was more like 13.” He attributed most of that difference to the more frequent vis-

its by the aflibercept group, at least in the first six months.

## REFERENCE

1. Baker CW, Glassman AR, Beaulieu WT, et al, for the DRCR Retina Network. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: A randomized clinical trial. *JAMA*. 2019 Apr 29. [Epub ahead of print]

## ASRS Scientific Meeting packs more into fewer days, leaders say

The 37th annual scientific meeting of the American Society of Retina Specialists, July 26 to 30 in Chicago, will be a day shorter than previous meetings, but program chair Carl C. Awh, MD, says that won't detract from the program.

“The heart of our meeting will continue to provide peer-reviewed research presented by ASRS members, but presentations will be shortened to allow more time for discussion,” Dr. Awh tells *Retina Specialist*.

This year's program includes the addition of expert “Take-Home Panels” to cover daily practice issues outside the scope of the peer-reviewed presentations. Another new offering Dr. Awh notes: “For the first time, ASRS will present a ‘Live Surgery Symposium,’ beaming world-renowned surgeons working in three different countries directly into the lecture hall.”

The final session on July 30 is titled “The Last Word,” which Dr. Awh describes as “a special panel discussion in which select presenters, nominated during the meeting by the audience and judges, will be given additional time to discuss the

most controversial, fascinating and important topics of the meeting.”

ASRS President John S. Pollock, MD, says the meeting will offer attendees several options for exchanging ideas. “There will be numerous opportunities for meaningful discussions with audience participation throughout the meeting, with highlights being the medical and surgical case conferences, the live surgery program and, during the scientific session, Q&A periods,” he says.

Social events will include the Welcome Reception on the evening of July 26 and the Black Tie Gala at the Field Museum of Natural History on July 28. The Hyatt Regency in Chicago is the headquarters hotel for ASRS.

On the day before ASRS starts, the Ophthalmology Innovation Summit—a conference that attracts drug and technology companies with innovations in all stages of development—will host OIS@ASRS at the Ritz-Carlton Chicago. The program includes showcases by public and private retina companies, along with panels on gene therapy, drug delivery and artificial intelligence. 

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# Insidious effect of HCQ therapy

*This case illustrates the importance of follow-up and multimodal imaging in managing retinal toxicity.*

**By Ravi R. Pandit,  
MD, MPH and  
Jason Hsu, MD**



**Department Editor  
Jason Hsu, MD**

**A** 46-year-old Caucasian woman presented in 2015 for routine follow-up three years after her last examination. She had no other visual concerns.

Her medical history was notable for systemic lupus erythematosus (SLE) which was well controlled on hydroxychloroquine (HCQ) for the past 23 years. At her previous visit in 2012, before loss to follow-up, she was noted to have normal retinal morphology and function by multimodal imaging and functional testing.

On re-examination, visual acuity was 20/20 and 20/30 in the right and left eyes, respectively. Anterior segment examination was unremarkable. Fundus appearance, spectral domain optical coherence tomography (SD-OCT), fundus auto-fluorescence (FAF) and automated visual fields are shown in Figures 1 to 3.

## HCQ retinal toxicity

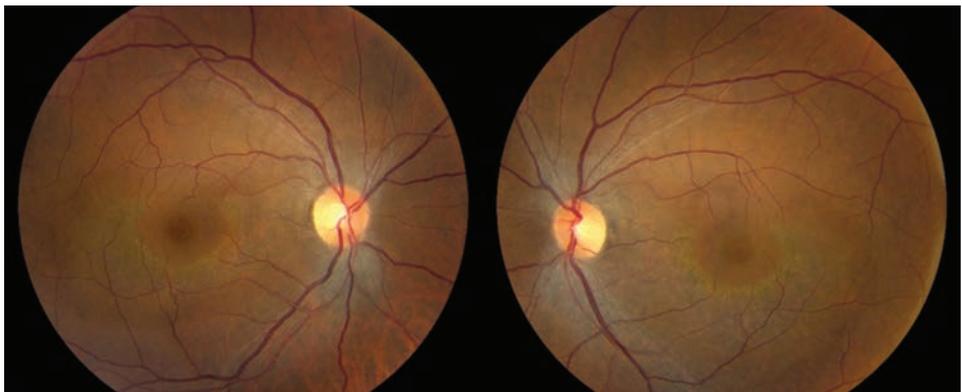
She was diagnosed with HCQ retinal toxicity, her rheumatologist was contacted and immediate HCQ cessation was recommended. She was switched to azathioprine, and the importance of regular ophthalmologic follow-up was emphasized.

The patient was lost to follow-up for three more years and presented again in 2018 with a chief concern of progressive blurred vision in both eyes. She noted that the azathioprine she was taking didn't control her lupus as well as HCQ. Visual acuity was 20/30 in both eyes and multimodal imaging demonstrated progressive HCQ toxicity in both eyes (*Figure 3C, page 12*). Continued HCQ avoidance was recommended, a letter was sent to her rheumatologist and regular ophthalmologic follow-up was again emphasized.

## HCQ use to increase

HCQ was initially developed in the 1960s as an anti-malarial agent and is now used for a wide range of autoimmune disorders, including SLE, rheumatoid arthritis and mixed connective tissue disorders.<sup>1</sup> The use of HCQ in SLE has been demonstrated to reduce the frequency of disease flares, renal disease, central nervous system involvement, thromboembolic events and mortality.<sup>2,3</sup>

Increasingly, the robust anti-inflammatory properties of HCQ are being investigated in dermatologic, cardiovascular, endocrine and oncologic diagnoses.<sup>2,4</sup>



**Figure 1.** Color fundus photographs of both eyes demonstrate characteristic “bull's-eye maculopathy” caused by retinal pigment epithelial changes in the perifoveal region. These findings are indicative of late hydroxychloroquine toxicity.

## Bios

Drs. Pandit and Hsu are with Mid-Atlantic Retina / Retina Service, Wills Eye Hospital, Philadelphia.

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

**Table 1. Risk factors for hydroxychloroquine retinal toxicity<sup>4</sup>**

Major risk factors		Minor risk factors	
Daily dosage	>5 mg/kg absolute body weight	Age	Older tissues may be less resistant to toxic effects
Duration of use	>5 years (if no other risk factors)	Liver disease	Some hepatic involvement in drug metabolism
Renal disease	Abnormal glomerular filtration rate (race and age dependent, typically <60 ml/min)	Genetic factors	Cytochrome P450 polymorphisms or inherited macular disease (eg, ABCA <sub>4</sub> mutations) may confer higher susceptibility to toxicity
Concomitant drugs	Tamoxifen use		
Macular disease	May impact susceptibility to toxicity or ability to monitor for toxicity		

Approximately 35,000 Americans were taking HCQ in 2016.<sup>5</sup> Given its favorable therapeutic profile in a broad range of conditions, the long-term use of HCQ is expected to grow, particularly among SLE patients for whom many physicians now advocate early HCQ initiation. In this context, the burden often falls to the ophthalmologist to screen for vision-threatening HCQ retinopathy and recommend cessation of this life-altering and life-saving medication when such toxicity develops.<sup>1,5</sup>

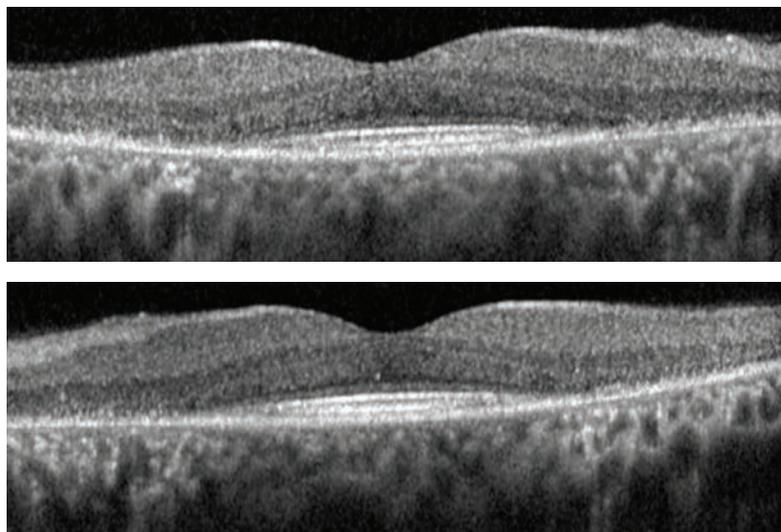
The exact mechanism of HCQ retinal toxicity isn't well understood, although multiple *in vivo* and *in vitro* studies have implicated drug accumulation in the retinal pigment epithelium and pigmented ocular tissues, often at levels thousands of times higher than serum. This can lead to relentless retinal dysfunction that can continue even after cessation of HCQ therapy.<sup>1,4,6</sup>

Progression of retinopathy has been documented up to three years after discontinuation of the drug, further emphasizing the importance of early identification of toxicity, well before the characteristic ring of parafoveal RPE depigmentation ("bull's-eye") appears.<sup>7</sup> It remains unclear why the foveal region is particularly susceptible to toxicity.<sup>1</sup>

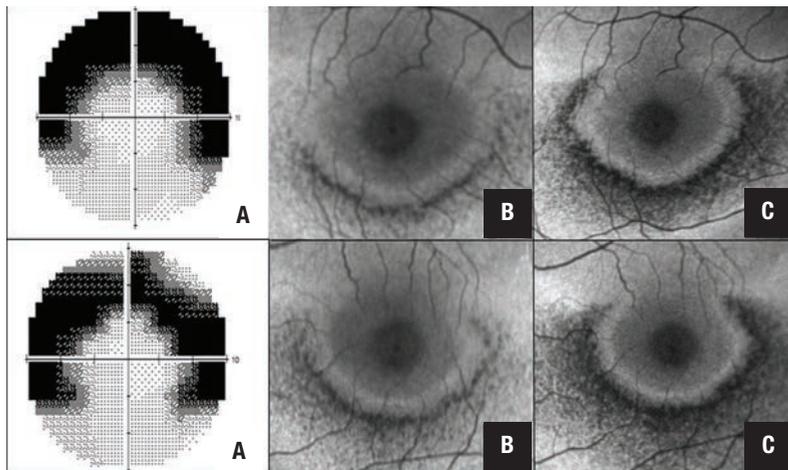
### Duration increases risk

The risk of HCQ toxicity increases with duration of use, with 7.5 (by SD-OCT and 10-2 VF criteria) to 33 percent (by multifocal electroretinography [mfERG] criteria) of individuals developing toxicity at five years.<sup>5</sup>

Daily dosing level is the most critical determinant of risk as well as the only modifiable one. At 25 years, patients taking HCQ <4 mg/kg had a 10 percent risk



**Figure 2. Spectral domain optical coherence tomography of both eyes (right eye, top; left eye, bottom) shows the characteristic "flying saucer sign" caused by perifoveal ellipsoid zone loss with preservation of the outer retina beneath the fovea indicative of late hydroxychloroquine toxicity.**



**Figure 3.** 10-2 visual field (A, right eye, top; left eye, bottom) demonstrates paracentral visual field loss. Fundus autofluorescence (B, 2015; C, 2018) demonstrates progressive retinal pigment epithelial death (hypoautofluorescence) in a “bull’s-eye” pattern. These findings are indicative of late hydroxychloroquine toxicity and reveal ongoing toxicity three years after HCQ cessation.

of developing retinopathy compared to a 65 percent risk in those taking  $>5$  mg/kg.<sup>4</sup>

Unfortunately, multiple studies support that a significant proportion of patients (13 to 75 percent) continue to receive toxic dosing, arising mostly from the use of outdated and unreliable ideal body weight calculations to ascertain safe daily dosing. For this reason, a number of medical societies now recommend 5 mg/kg of absolute body weight to calculate maximum safe dose of HCQ.<sup>4</sup>

### Managing HCQ toxicity risk

A smartphone application called Dose-checker, developed by Elliot M. Perlman, MD, and colleagues, has been reported to reduce the burden of manually calculating a low-risk HCQ dosing regimen for their patients.<sup>8</sup> The application is available for both Apple and Android devices.

Other “major risk factors” include renal disease—as frequently found in rheumatologic conditions—and tamoxifen use (a fivefold increased risk of toxicity) for reasons that are yet unclear. Preexisting retinal and macular disease have also been cited as major risk factors, but no specific data supports this assertion.

### Avoiding retinotoxic agents

Nevertheless, avoiding a retinotoxic agent in an already diseased retina seems reasonable, and preexisting retinal disease may interfere with the ability to detect early or subtle changes associated with HCQ toxicity. The absence of evidence also implies that isolated macular findings (eg, single drusen) may not be reasonable alone to withhold HCQ necessary to control systemic disease.

Age, hepatic disease and genetic factors (eg, ABCA4 or cytochrome P450 polymorphisms) are considered “lesser risk factors,” in that biologic plausibility exists but no definitive evidence that they contribute to toxicity.<sup>4</sup> Table 1 (page 11) summarizes the risk factors set forth by the American Academy of Ophthalmology in 2016.

### Bottom line

While HCQ toxicity can’t be reversed, it can be identified preclinically before symptomatic vision loss occurs.<sup>4</sup> In the context of increasing use and persistently high-dosing regimens, universal screening HCQ-associated retinal toxicity is recommended for all HCQ users in the United States.<sup>5</sup>

The AAO released its revised guidelines for HCQ retinopathy screening in 2016.<sup>4</sup> Prior surveys of ophthalmologists and rheumatologists have revealed incomplete understanding and implementation of AAO guidelines, which could result in HCQ toxicity or inappropriate cessation of a highly beneficial medication.<sup>1,6</sup> We summarize the 2016 AAO guidelines (*opposite page*) for further review.

### REFERENCES

1. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. *Eye*. 2017;31:828-845.
2. Alarcon GS, McGwin G, Bertoli AM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis*. 2007;66:1168-1172.
3. Fessler BJ, Alarcón GS, McGwin G, et al. Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. *Arthritis*

## 2016 American Academy of Ophthalmology Guidelines for HCQ Retinopathy<sup>4</sup>

### Frequency of Screening

**Baseline examination**—All patients starting long-term hydroxychloroquine (HCQ) should undergo a full ophthalmologic evaluation within one year of starting the medication, with particular emphasis on identifying macular disease that may predispose to retinopathy or limit interpretation of screening tests. In the setting of a normal fundus examination, baseline spectral-domain optical coherence tomography (SD-OCT) or visual fields are not required. This initial visit is an opportunity to educate prescribers and users of HCQ about safe dosing and the importance of regular screening.

**Annual Screening**—In absence of major risk factors, annual screening can be deferred until five years of HCQ use. However, screening should occur sooner than five years if major risk factors exist. At each screening visit, dosage relative to weight should be calculated, and the patient should be queried about changes related to major risk factors.

### Screening Tests

Automated VF is a highly sensitive test of retinal function, though there is wide variation in testing reliability; multiple VF or user-independent tests like multifocal electroretinography (mfERG) may be required to confirm true pathology. Damage often—but not always—begins in the inferotemporal macula resulting in a superior-nasal visual field defect. Visual field defects may manifest before apparent structural damage.<sup>4</sup> Of note, there are racial differences in distribution of retinal damage, with up to 50 percent of Asian patients exhibiting a pericentral damage in the region of the vascular arcades in contrast to 2 percent of Caucasian patients. Accordingly, 10-2 and 30-2 VF patterns are recommended for Caucasian and Asian patients, respectively.<sup>9</sup>

SD-OCT is an objective, structural test that can detect early toxicity by identifying localized thinning of the photoreceptor layers, often recognized as focal interruptions of the ellipsoid zone, well before retinal pigment epithelium loss develops. As above, wide-field OCT may detect similar pericentral changes in Asian patients. Fundus auto-fluorescence may reveal hyper-autofluorescence in areas of photoreceptor damage even prior to photoreceptor thinning on SD-OCT.

Fundus photography, time-domain OCT, fluorescein angiography, full-field ERG, Amsler grid, color vision testing and electro-oculogram are not recommend for screening.

**Table 2. Screening recommendations for hydroxychloroquine retinal toxicity<sup>4</sup>**

Frequency		Testing	
<b>Baseline</b>	Fundus examination within one year of starting medication. Visual field or spectral domain optical coherence tomography indicated if preexisting maculopathy is detected.	<b>Primary</b>	VF (24-2 or 30-2 pattern in patients of Asian ancestry, 10-2 pattern in others) and SD-OCT.
<b>Annual</b>	Begin after five years of use, sooner if other major risk factors exist.	<b>Secondary</b>	Fundus auto-fluorescence or multifocal electroretinogram as needed to confirm pathology.

However, some of these modalities may be useful in documentation of late-stage toxicity.

Adaptive optics and OCT angiography promise to objectively, non-invasively, and more completely image macular photoreceptors and vasculature, although the use of both in HCQ screening are presently investigational.<sup>10</sup> Early studies have demonstrated increased foveal avascular zone, reduced retinal and choroidal flow, and reduced choroidal thickness in high- vs. low-risk patients taking HCQ.<sup>10</sup>

Screening frequency and testing recommendations are summarized in Table 2.

### Management

Beyond cessation of the offending medication, there is no proven treatment to prevent, mitigate or treat HCQ retinopathy. This underscores the importance of ongoing interdisciplinary communication, aggressive risk factor identification/modification, appropriate screening and prompt HCQ discontinuation if signs of toxicity become evident. 

Rheum. 2005;52:1473-1480.

4. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology*. 2016;123:1386-1394.

5. Browning DJ. The prevalence of hydroxychloroquine retinopathy and toxic dosing, and the role of the ophthalmologist in reducing both. *Am J Ophthalmol*. 2016;166:ix-xi.

6. Shulman S, Wollman J, Brikmann S, Padova H, Elkayam O, Paran D. Implementation of recommendations for the screening of hydroxychloroquine retinopathy: Poor adherence of rheumatologists and ophthalmologists. *Lupus*. 2017;26:277-281.

7. Marmor MF, Hu J. Effect of disease stage on progression of

hydroxychloroquine retinopathy. *JAMA Ophthalmol*. 2014;132:1105.

8. Perlman E, Friday R, Greenberg P, Browning D, Miller J. Dosechecker: Solving the hydroxychloroquine dosing dilemma with a smart phone app [abstract]. *Arthritis Rheumatol*. 2017; 69 (suppl 10) <https://acrabstracts.org/abstract/dosechecker-solving-the-hydroxychloroquine-dosing-dilemma-with-a-smart-phone-app/>. Accessed February 24, 2019.

9. Melles RB, Marmor MF. Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. *Ophthalmology*. 2015;122:110-116.

10. Bulut M, Akıdan M, Gözkaya O, Erol MK, Cengiz A, Çay HF. Optical coherence tomography angiography for screening of hydroxychloroquine-induced retinal alterations. *Graefes Arch Clin Exp Ophthalmol*. 2018;256:2075-2081.

# How OCT is aiding uveitis management

*Optical coherence tomography helps grade inflammation and evaluate the vitreous, retinal vasculature and choroid.*



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

**O**ptical coherence tomography is an indispensable tool for the diagnosis and management of patients with uveitis. Use of OCT in uveitis is most often directed at monitoring for retinal complications such as cystoid macular edema, epiretinal membranes, subretinal fluid, secondary choroidal neovascularization and inner/outer retinal and retinal pigment epithelium disruption. There are, however, a few more seldom-recognized ways to use OCT in the uveitic patient. I'll review them here.

## Grading AC inflammation

Multiple studies have shown the potential for the use of anterior segment OCT in the grading of anterior chamber inflammation.<sup>1,2</sup> In a study by Sumit Sharma, MD, and colleagues, the number of cells seen on AS-OCT line and volume scans strongly correlated with the number of cells seen on clinical examination.<sup>1</sup>

A later study by Alessandro Invernizzi, MD, and colleagues additionally used swept-source OCT for the grading of anterior chamber flare.<sup>2</sup> They used AS-OCT images to calculate an absolute value of aqueous signal intensity, comparing that value to the signal measured outside the eye to arrive at an aqueous-to-air relative inten-

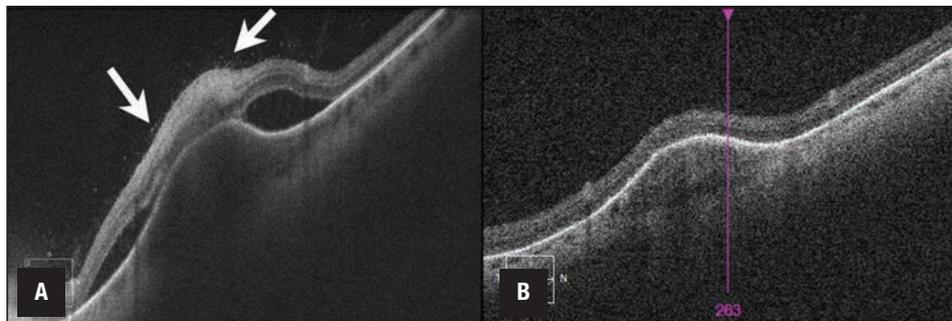
sity index. The researchers found that the ARI index rose with increasing clinical flare measurements and correlated with laser flare photometry measurements in patients with active uveitis.

## Evaluation of the vitreous

Evaluation of vitreous cells relies on slit-lamp examination and only looks for inflammation in the anterior vitreous. Because anterior uveitis can result in spillover involvement of the anterior vitreous, the presence of anterior vitreous cells alone does not typically signify a vitritis. Thus, in the absence of visible snowballs or snowbanks, the presence of an overt vitritis can be called into question.

Additionally, the presence of anterior media opacities can make evaluation of the anterior vitreous challenging and confound the grading of vitreous haze. OCT allows routine examination of the posterior cortical vitreous, in which posterior vitreous cells appear as hyper-reflective spots.

Evaluation of cells in the posterior vitreous can provide important diagnostic information. For example, in the case of an elevated choroidal lesion, presence of overlying vitreous hyper-reflective spots on OCT could signify an inflammatory rather than malignant lesion (*Figure 1*). Addi-



**Figure 1. Optical coherence tomography line scans through an elevated choroidal lesion before (A) and after (B) treatment with oral steroids. Note the hyper-reflective opacities in the posterior cortical vitreous (arrows), suggestive of an overlying vitritis.**

## Bio

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

**DISCLOSURE:** Dr. Thomas has no relevant financial relationships to disclose.

tionally, improvement in such a posterior vitreous cell count can be used to monitor response to therapy.

While other vitreous opacities, such as vitreous hemorrhage, may be indistinguishable on OCT, *in vitro* data suggest that cell reflectance for various cell types (neutrophils, monocytes, lymphocytes, erythrocytes) may in fact be different.<sup>3</sup> In addition to evaluating the posterior vitreous, OCT may be useful for evaluation of anterior vitreous cell and vitreous haze. A clinical trial is currently recruiting patients to evaluate this very question.<sup>4</sup>

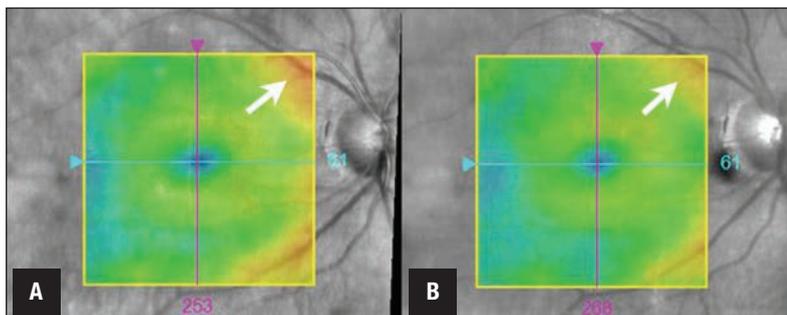
### Evaluation of the retinal vasculature

Determining the presence of retinal vasculitis is largely predicated on ophthalmoscopy and fluorescein angiography. However, evaluation of OCT thickness maps can be a valuable adjunct for monitoring retinal vasculitis. A 2018 study reported that perivascular thickening on OCT thickness maps may be a marker of retinal vasculitis in uveitides featuring a large vessel retinal vasculitis, such as birdshot chorioretinopathy (*Figure 2*).<sup>5</sup> The same study showed that the severity of such perivascular thickening corresponded to the severity of perivascular leakage on FA, was independent of CME and central macular thickness, and improved in response to therapy.

### Evaluation of the choroid

Enhanced-depth imaging (EDI)-OCT enables evaluation of the choroid, which can prove very informative when managing uveitis. Increased choroidal thickness has been noted in eyes with acute anterior uveitis compared to fellow uninvolved eyes<sup>6</sup> and eyes of patients without uveitis.<sup>7</sup> Additionally, one study noted that choroidal thickness decreased with therapy.<sup>6</sup>

Increased choroidal thickness has not been noted in all forms of anterior uveitis. One study found that eyes with HLA-B27-associated anterior uveitis



**Figure 2. Optical coherence tomography thickness map (A) shows perivascular thickening (arrow) in a patient with birdshot chorioretinopathy. After intravitreal triamcinolone acetonide, the perivascular thickening improved (B).**

showed similar choroidal thickness values to eyes without uveitis.<sup>7</sup> Another series found that eyes with Fuchs' heterochromic iridocyclitis had choroidal thinning relative to fellow uninvolved eyes.<sup>8</sup>

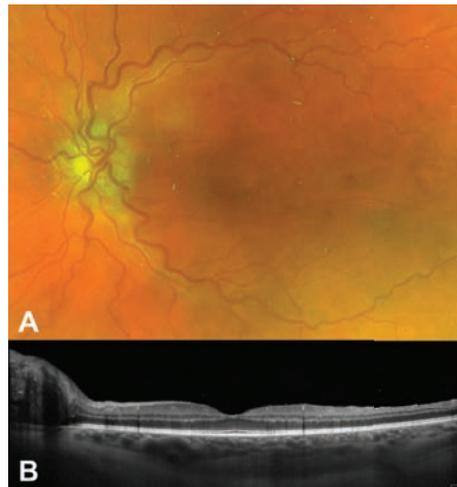
Choroidal thickening has also been shown to correspond to disease activity in eyes with active uveitis secondary to Behçet's disease.<sup>9,10</sup> Additionally, a reduction in choroidal thickness was noted among these patients, with therapy corresponding to other clinical measures of inflammatory control.<sup>9,10</sup> One study found that the choroidal thickness in BD decreased with greater duration of disease activity, suggesting that prolonged choroiditis results in choroidal thinning.<sup>11</sup>

Vogt-Koyanagi-Harada disease can cause choroidal thickening with or without serous retinal detachment. Similar to BD, treatment of inflammation in VKH can cause a corresponding reduction in choroidal thickening (*Figure 3, page 16*).<sup>12,13</sup> Interestingly, the choroidal thickening in VKH seems to correspond to a thickening of the choroidal stroma rather than engorgement of the choroidal vasculature.<sup>14</sup>

Many uveitides feature a multifocal rather than diffuse choroiditis. In eyes with extensive choroidal lesions, monitoring for the development of new lesions can be cumbersome. Lesions may not be readily evident on ophthalmoscopy, may rely on

**Determining the presence of retinal vasculitis is largely predicated on ophthalmoscopy and fluorescein angiography.**

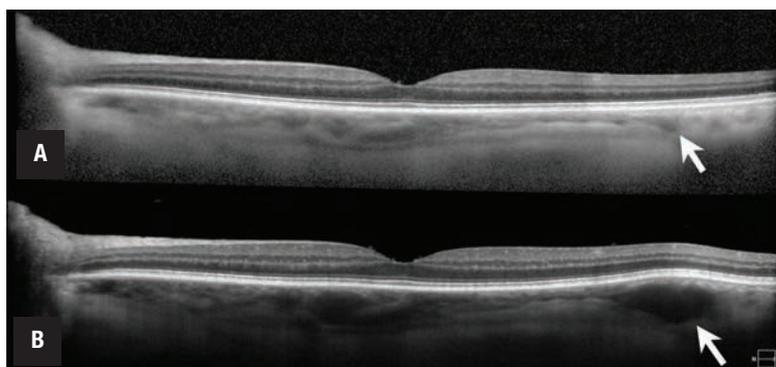
**Figure 3. Pseudocolor photo (A) of the fundus of a patient presenting with optic nerve swelling. Enhanced-depth-imaging optical coherence tomography revealed choroidal thickening (B). The patient subsequently developed serous retinal detachment and was diagnosed with Vogt-Koyanagi-Harada disease.**



indocyanine green angiography and may not always correspond with other markers of disease activity. EDI-OCT can allow for the monitoring of new macular and peripapillary choroidal lesions and the response of such lesions to therapy (Figure 4).<sup>15</sup>

### Bottom line

Overall, potential uses for OCT in the diagnosis and management of uveitis continue to expand, although several of the aforementioned expanded clinical applications of OCT rely on manual measurements (choroidal evaluation), automated algorithms that aren't widely available (anterior chamber inflammation measurements), semi-quantitative measurements



**Figure 4. Enhanced-depth-imaging optical coherence tomography line scans of a patient with multifocal choroiditis due to sarcoidosis. Note the presence of a small choroidal lesion (A, arrow) that enlarged two months later (B, arrow).**

(perivascular thickening analysis) and evaluations for which longitudinal changes may be challenging (posterior vitreous cell measurements).

Given the heterogeneity of uveitis, no single imaging modality can adequately quantify the degree of inflammation across all of its forms. OCT, however, has the potential to measure inflammation and inflammatory sequelae in ocular structures beyond the retina. <sup>15</sup>

### REFERENCES

- Sharma S, Lowder CY, Vasanthi A, Baynes K, Kaiser PK, Srivastava SK. Automated analysis of anterior chamber inflammation by spectral-domain optical coherence tomography. *Ophthalmology*. 2015;122:1464-1470.
- Invernizzi A, Marchi S, Aldigeri R, et al. Objective quantification of anterior chamber inflammation: Measuring cells and flare by anterior segment optical coherence tomography. *Ophthalmology*. 2017;124:1670-1677.
- Rose-Nussbaumer J, Li Y, Lin P, et al. Aqueous cell differentiation in anterior uveitis using Fourier-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2015;56:1430-1436.
- Optical coherence tomography (OCT) in uveitis. *ClinicalTrials.gov* identifier NCT02026128. <https://clinicaltrials.gov/ct2/show/NCT02026128?term=NCT02026128&rank=1>. Accessed May 15, 2019.
- Thomas AS, Hatef AL, Stinnett SS, Keenan RT, Jaffe GJ. Perivascular thickening on optical coherence tomography as a marker of inflammation in birdshot retinochoroiditis. *Retina*. 2019;39:956-963.
- Gabriel M, Kruger R, Shams-mafi F, et al. Mapping retinal and choroidal thickness in unilateral nongranulomatous acute anterior uveitis using three-dimensional 1060-nm optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2017;58:4778-4783.
- Kim M, Choi SY, Park YH. Analysis of choroidal and central foveal thicknesses in acute anterior uveitis by enhanced-depth imaging optical coherence tomography. *BMC Ophthalmol*. 2017;17:225.
- Cerquaglia A, Iaccheri B, Fiore T, et al. Full-thickness choroidal thinning as a feature of Fuchs uveitis syndrome: Quantitative evaluation of the choroid by enhanced depth imaging optical coherence tomography in a cohort of consecutive patients. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:2025-2031.
- Ishikawa S, Taguchi M, Muraoka T, Sakurai Y, Kanda T, Takeuchi M. Changes in subfoveal choroidal thickness associated with uveitis activity in patients with Behçet's disease. *Br J Ophthalmol*. 2014;98:1508-1513.
- Kim M, Kim H, Kwon HJ, Kim SS, Koh HJ, Lee SC. Choroidal thickness in Behçet's uveitis: An enhanced depth imaging-optical coherence tomography and its association with angiographic changes. *Invest Ophthalmol Vis Sci*. 2013;54:6033-639.
- Park UC, Cho IH, Moon SW, Yu HG. Long-term change of subfoveal choroidal thickness in Behçet's disease patients with posterior uveitis. *Ocul Immunol Inflamm*. 2018;26:397-405.
- Kawano H, Sonoda S, Yamashita T, Maruko I, Iida T, Sakamoto T. Relative changes in luminal and stromal areas of choroid determined by binarization of EDI-OCT images in eyes with Vogt-Koyanagi-Harada disease after treatment. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:421-426.
- Jap A, Chee SP. The role of enhanced depth imaging optical coherence tomography in chronic Vogt-Koyanagi-Harada disease. *Br J Ophthalmol*. 2017;101:186-189.
- Li M, Liu Q, Luo Y, et al. Enhanced depth SD-OCT images reveal characteristic choroidal changes in patients with Vogt-Koyanagi-Harada disease. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47:1004-1012.
- Böni C, Thorne JE, Spaide RF, et al. Choroidal findings in eyes with birdshot chorioretinitis using enhanced-depth optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2016;57:591-599.

# Novel approach to traumatic macular hole

*Human amniotic membrane is used to create a scaffold-like structure to close a large hole.*

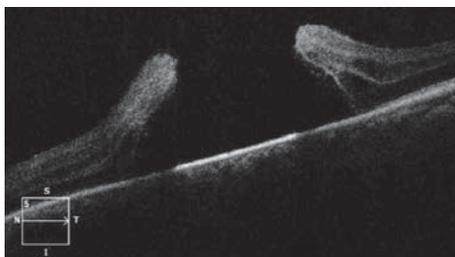
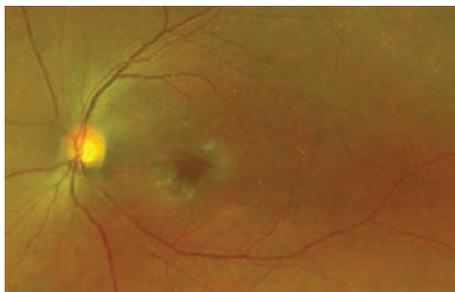
**A** large traumatic macular hole poses a challenge to the vitreoretinal surgeon, because both characteristics—large and traumatic—are associated with lower surgical closure rates. The mechanism of traumatic macular hole formation is more likely to result in avulsed tissue, and even after vitrectomy with wide internal limiting membrane peel, the hole may not successfully close.

## Human amniotic membrane scaffold

Newer techniques have been developed to address macular holes with lower likelihood of closure. Stanislao Rizzo, MD, and colleagues at the University of Florence in Italy recently reported on a technique that uses human amniotic membrane (HAM) placed in the subretinal space to bridge the tissue gap and provide a scaffold which the surrounding retinal tissue can overfill to successfully close the macular hole.<sup>1</sup>

At the University of Colorado, this technique was employed in the repair of a >1,200 µm traumatic macular hole with a stellate configuration (*Figure 1*). A traditional 25-gauge vitrectomy setup was employed with indocyanine-green-assisted ILM peeling. A multi-segment centripetal ILM peel was performed due to the stellate nature of the traumatic macular hole, paying careful attention to avoid radialization of the leaflets or enlarging of the hole.

The HAM utilized was AmnioGraft (Bio-Tissue), a cryopreserved placental tissue with inactivated cell bioactivity. AmnioGraft is classically used for ocular



**Figure 1. Views of a large stellate traumatic macular hole >1,200 µm.**

surface cases such as pterygium excision and Stevens Johnson Syndrome.

## Trim and introduce

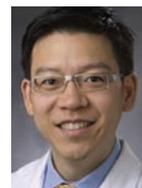
In this procedure, the HAM tissue outside the eye was trimmed to a 1.5-x-1.5-mm patch (slightly larger than the hole), gathered within the serrated forceps tines and introduced via the standard 25-ga. cannula with the valve removed for smooth entry.

The edges of the macular hole were gently elevated with injection of viscoelastic, and the HAM was introduced into the subretinal space. Within the fluid-filled vitreous cavity, the HAM was easily manipulated, unfurled and navigated into appropriate position. A small amount of viscoelastic (Healon) was injected over the HAM as a tamponade to maintain the placement of the graft.

## Careful air-fluid exchange

Next, a standard air-fluid exchange was performed with careful aspiration directly  
*(Continued on page 38)*

**By Marisa Lau, MD,  
and Jesse Smith, MD**



**Department Editor  
Paul Hahn,  
MD, PhD**

## View the Video



Drs. Lau and Smith demonstrate closure of a large traumatic macular hole with human amniotic membrane graft. Available at: [http://bit.ly/VideoPearl\\_010](http://bit.ly/VideoPearl_010)

## Bios

Dr. Hahn is a partner at New Jersey Retina in Teaneck. Dr. Lau is a vitreoretinal surgery fellow at the University of Colorado, Denver. Dr. Smith is an assistant professor of ophthalmology there.

**DISCLOSURES:** Dr. Hahn is a consultant to Alcon.

## New Horizons in Drug Delivery

# The hands-on technique for suprachoroidal injection

*Xipere is on track for FDA approval later in the year. Here's a stepwise approach for using the injector successfully.*



Mark Barakat, MD

By Mark Barakat, MD

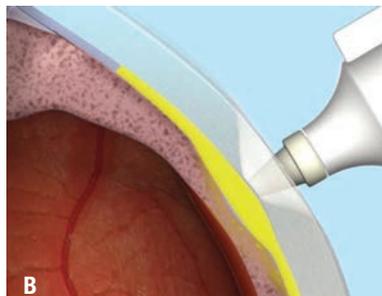
### Take-home points

- » Using Xipere (triamcinolone acetonide) injection to deliver drug to the suprachoroidal space is somewhat different from doing intravitreal injections.
- » Holding the microinjector perpendicular to the sclera and applying constant, firm pressure on the plunger are essential steps.
- » The first time receiving Xipere, patients require a thorough explanation on what to expect.

**X**ipere (Clearside Biomedical) is triamcinolone acetonide ophthalmic suspension for suprachoroidal injection. It met its primary endpoint in Phase III trials for macular edema associated with uveitis and Phase II study for diabetic macular edema. In February, the Food and Drug Administration accepted the new drug application for the uveitis indication and assigned a Prescription Drug User Fee Act date of October 19.

Xipere is delivered to the suprachoroidal

space using a proprietary injector for the treatment of macular edema associated with noninfectious uveitis. The advantage of targeting the suprachoroidal space is that it distributes the drug more directly to the retina and choroid, sparing the anterior chamber. This delivers higher drug concentrations to the parts of the eye where it is most needed, with the potential to decrease the negative side effects typical of steroid therapy, such as cataract formation and increased intraocular pressure.



**Figure. A)** Maintaining constant, firm pressure on the plunger throughout the injection is key to using the Xipere microinjector. **B)** Holding the Xipere microinjector needle perpendicular to the sclera, dimple down on the sclera 4 to 5 mm from the limbus. (Images courtesy Clearside Biomedical)

### Three key principles for use

While the injector is designed to facilitate the safe delivery of triamcinolone to the suprachoroidal space, the technique does differ from your typical intravitreal injection. When administering Xipere, three principles are paramount:

- Hold the injector perpendicular to the sclera.
- Maintain constant, firm pressure on the plunger throughout (Figure A) and dimple down on the sclera (Figure B),
- Inject slowly and consistently.

Here, I'll discuss the process of administering Xipere in the clinic.

### Patient prep

As a frame of reference, it may help to understand how a Xipere injection differs from an intravitreal triamcinolone injection.

While I typically use subconjunctival lidocaine for most of my IVT as a matter of preference, I find it more important for the suprachoroidal injection, as the whole process does take somewhat longer. I find the use of a lid speculum optional for IVT in most patients, as I am able to isolate the lids with my free hand.

With Xipere, the injector is designed with a two-handed approach in mind; thus I find the speculum to be very helpful. While holding the injector like a pen in my dominant hand and applying and maintaining gentle, but firm, pressure on the plunger with the other, the speculum plays a critical role in keeping the lids at bay.

The first time receiving a Xipere injection, patients don't know what to expect. It may be helpful to have a brief dialog with them. Some patients may notice a degree of injection-site discomfort, typically transient in nature and resolving without treatment. Injecting slowly and consistently can minimize this discomfort. Most will notice pressure during the injection, more so than with IVT, as the hub of the suprachoroidal injector is firmly applied to the surface.

### The act of the injection

When approaching the eye with the injector, the angle is critical. The injector must be perpendicular to the sclera in order to penetrate it and advance the needle tip into the suprachoroidal space. With IVT, the angle of the needle isn't as critical, the needle being several times longer than necessary to reach the vitreous cavity.

With Xipere, the injector needle is specifically designed with the thickness of the sclera in mind: only by approaching at a perpendicular angle, fully inserting the needle, and applying pressure at the hub (creating

a scleral dimple at the injection site), the needle is able to clear the sclera and reach the correct anatomic space.

Place the needle 4 to 5 mm from the limbus, in approximately the same spot as an IVT. The injector is very intuitive. As soon as you enter sclera, hold and maintain constant pressure on the plunger with your non-dominant hand. While the tip of the needle is still in the dense sclera, the outflow resistance is high, preventing injection in the wrong plane. Upon reaching the suprachoroidal space, you feel a loss of resistance and the medication is delivered. Continue to firmly apply pressure with the hub of the injector on to the sclera for about five seconds after injection. This pressure helps prevent reflux of the triamcinolone.

I have found the learning curve for this technique to be brief. As long as the needle tip is positioned correctly and the pressure on the plunger is constant, the triamcinolone should reliably reach the suprachoroidal space.

While inadvertent intravitreal injections have been reported, they are rare. As long as the injection is done at a pars plana location (4 to 5 mm from the limbus) this should pose no more challenge than your typical IVT, although it may be helpful to prepare the patient for the possibility ahead of time. Of much greater potential clinical concern is suprachoroidal hemorrhage, which remains theoretical only in nature; it has never been noted with this technique during any clinical trial.

### The bottom line

In the near future, Xipere may become an important addition to the retina specialist's toolbox for treatment of uveitis and possibly DME. With the very convincing Phase III data for its use in the treatment of uveitis-associated macular edema, it behooves all of us to become familiar with the suprachoroidal injection approach. This will allow us as clinicians to offer a complete array of treatment options, to the benefit of our patients. 

**As long as the needle tip is positioned correctly and the pressure on the plunger is constant, the triamcinolone should reach the suprachoroidal space.**

### Bio

Dr. Barakat is physician at Retina Consultants of Arizona, Phoenix.

**DISCLOSURE:** Dr. Barakat disclosed he is a consultant to Alimera Sciences, Allegro Ophthalmics, Genentech, Novartis and RegenxBio. He also owns stock in Oxurion and Ohr Pharmaceutical.

## New Horizons in Drug Delivery

# The promise of PDS in real-world practice

*Lessons from the Ladder trial of the Port Delivery System with ranibizumab (PDS) and what the Archway trial will aim to confirm.*

By Nazrul I. Mojumder, MS, Sylvia Phillips, BA, CCRP,  
and Arshad M. Khanani, MD, MA



Nazrul I.  
Mojumder, MS



Sylvia Phillips,  
BA, CCRP



Arshad M.  
Khanani, MD,  
MA

## Bios

Mr. Mojumder is a medical student at the University of Nevada, Reno School of Medicine.

Mrs. Phillips is assistant director of clinical research at Sierra Eye Associates, Reno.

Dr. Khanani is a clinical associate professor at the University of Nevada, Reno School of Medicine and managing partner and director of clinical research at Sierra Eye Associates.

## Take-home points

- » The Port Delivery System with ranibizumab (PDS) is inserted in the eye in the operating room and refilled during a minimally invasive in-office refill-exchange procedure.
- » The rate of release of ranibizumab is proportional to the concentration of the drug in the PDS.
- » The Phase III Archway study will be crucial to confirm the efficacy and safety of PDS in patients with neovascular age-related macular degeneration.

Anti-VEGF agents have revolutionized our treatment for patients with neovascular age-related macular degeneration, but they come with a high treatment burden due to frequent clinic visits as well as injections. In the real world, this burden on patients and family members results in missed clinical visits. Therefore, visual acuity gains seen in the clinical trials aren't maintained in clinical practice due to less than optimal dosing, and there is a direct correlation with number of injections and visual acuity gains.<sup>1,2</sup>

The treatment burden associated with anti-VEGF injection therapy and the ensuing suboptimal outcomes create an unmet need for more durable and lasting treatments. Considering the promising results of the Phase II Ladder trial, the Port Delivery System with ranibizumab (PDS, Genentech) holds great potential to address this unmet need.

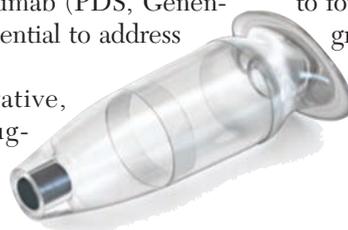
PDS is an innovative, investigational drug-delivery system that includes a surgically

placed implant for continuous delivery of a customized formulation of ranibizumab into the vitreous (*Figure 1*).<sup>3,4</sup> The PDS implant is surgically inserted at the pars plana in the operating room. The implant is refilled during a minimally invasive in-office refill-exchange procedure using the specially designed PDS refill needle (*Figure 2*).<sup>3,4</sup>

The release of drug from the PDS into the vitreous follows first-order kinetics. The rate of release is proportional to the concentration of the drug in the PDS.

## Lessons from Ladder trial

The Phase II Ladder (Long Acting Delivery of Ranibizumab) trial was designed to evaluate the treatment effect, durability and safety of the PDS. The primary analysis population consisted of 220 patients randomized to four different arms.<sup>5,6</sup> The three PDS groups received different concentra-



**Figure 1.** The Port Delivery System with ranibizumab (PDS) is about as large as a grain of rice. It's surgically implanted at the pars plana.

tions of ranibizumab (10 mg/mL, 40 mg/mL, 100 mg/mL), and the fourth group received monthly intravitreal injections of 0.5 mg ranibizumab.<sup>4,6</sup> The primary endpoint of the study was time to the first PDS refill.

Refill criteria were prespecified by the study protocol and were based on clinical features of disease activity. The key secondary endpoints were change from baseline in best corrected visual acuity, change from baseline in central foveal thickness (CFT) and safety of the PDS versus monthly ranibizumab injections.

In the initial months of study enrollment, a high rate of intraoperative and immediate postoperative vitreous hemorrhage was observed. The study was paused to find a way to mitigate this, then was resumed with a modified surgical procedure that included laser ablation of the pars plana before the implant was inserted. This modification resolved the issue of vitreous hemorrhage and the trial went on to successful completion.<sup>5,6</sup>

### Treatment burden reduced

The Ladder results were promising, showing that 80 percent of patients in the PDS 100-mg/mL arm went at least six months without requiring a refill.<sup>5,6</sup> The median time to first refill in this group was 15 months.<sup>5,6</sup>

Looking at visual acuity, PDS improved or maintained vision, as the adjusted vision outcomes at nine months were similar between PDS 100 mg/mL and monthly 0.5 mg ranibizumab injections.<sup>5,6</sup> The anatomic outcomes based on CFT were also similar between both groups.

As far as ocular and systemic safety of the PDS, the optimized implant insertion and refill procedures were well-tolerated. The Ladder study patients are being followed long term to look at efficacy and safety in the extension Portal study.<sup>7</sup>

### Next: Archway study

Based on the positive Phase II Ladder data, the Archway study was designed. Archway is a Phase III, randomized, multicenter, active-comparator study designed to assess

the efficacy, safety and pharmacokinetics of 100 mg/mL ranibizumab delivered via PDS with a fixed refill at week 24 compared with monthly ranibizumab treatment.<sup>8</sup>

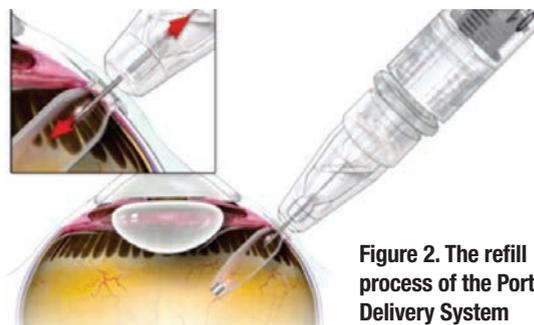
The study started in September 2018 and will enroll 360 patients. A surgical training plan, including virtual reality simulation, has been implemented for the ongoing Archway trial to ensure procedural consistency and prioritize patient safety. This virtual reality system simulates the PDS procedure and helps surgeons gain hands-on simulated experience before their first surgery and implant refill procedures in the study.

### Bottom line

Based on the data from the Ladder study, the PDS technology has the potential to improve real-world outcomes in our patients with neovascular AMD by addressing the unmet need of continuous delivery of anti-VEGF as well as decreasing treatment burden. The data from the Phase III Archway study will be crucial to confirm the efficacy and safety of PDS. 

### REFERENCES

1. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355:1419-1431.
2. Holz FG, Tadayoni R, Beatty S, et al. Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study. *Br J Ophthalmol.* 2016;100:1623-1628.
3. Krader CG, Regillo C. Decreasing burden of nAMD therapy. *Ophthalmology Times.* 2019;44 (1):27.
4. Press release: Genentech unveils positive Phase II results for the Port Delivery System with ranibizumab (PDS), the first-ever eye implant to achieve sustained delivery of a biologic medicine to treat people with wet age-related macular degeneration (AMD). July 2018. <https://www.genentech.com/media/press-releases/14739/2018-07-25/genentech-unveils-positive-phase-ii-resu>.
5. Pieramici D. Port Delivery System with ranibizumab (PDS): from dose ranging in Ladder phase 2 to ARCHWAY phase 3 study design. Presented at the 2018 American Academy of Ophthalmology Annual Meeting; Chicago, IL; October 27, 2018.
6. Regillo C. Sustained release ranibizumab therapy: PDS Phase 2 Ladder study. Presented at: Bascom Palmer Eye Institute Angiogenesis, Exudation, and Degeneration 2019 Meeting; Miami, FL; February 9, 2019.
7. Extension study for the Port Delivery System with ranibizumab (Portal). <https://clinicaltrials.gov/ct2/show/NCT03683251>. Accessed March 23, 2019.
8. A Phase III study to evaluate the Port Delivery System implant with ranibizumab compared with monthly ranibizumab injections in participants with wet age-related macular degeneration (Archway). <https://clinicaltrials.gov/ct2/show/NCT03677934>. Accessed March 23, 2019.



**Figure 2. The refill process of the Port Delivery System with ranibizumab (PDS) occurs in an in-office procedure. (Images courtesy Genentech)**

### Disclosures

Mr. Mojumder has no relevant financial relationships to disclose.

Mrs. Phillips is a consultant for Genentech.

Dr. Khanani is a consultant and speaker for Genentech and also receives research funding from Genentech.

## New Horizons in Drug Delivery

# A real-world experience administering gene therapy

*Multiple steps, including intraoperative optical coherence tomography, are involved in treating a pediatric eye with voretigene neparvovec-rzyl.*

By Nicolas Yannuzzi, MD, and Audina Berrocal, MD



Nicolas  
Yannuzzi, MD



Audina  
Berrocal, MD

### Take-home points

- » Administering voretigene neparvovec-rzyl in the subretinal space involves induction of the posterior vitreous detachment with staining to ensure the hyaloid is elevated.
- » Use of a microinjector improves control in deploying the gene vector compared with manual injection.
- » Intraoperative optical coherence tomography is useful in confirming subretinal delivery of the drug.

**V**oretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) is the first gene therapy approved for ocular use in patients with RPE65-mediated inherited retinal dystrophy. A Phase III trial found that the treatment was well-tolerated and resulted in a significant improvement in multi-luminance mobility testing. The drug, delivered in the subretinal space, has been administered in several centers.

Here, we hold a clinical conversation on the technical aspects of administering voretigene neparvovec-rzyl. On page 24, we also provide the perspective of the mother of one of our patients.

### Choosing instrumentation

**Nicolas Yannuzzi, MD:** *What gauge instrumentation do you use for these cases?*

**Audina Berrocal, MD:** I use the 25-gauge EVA vitrectomy pack (DORC) system.

**NY:** *Posterior vitreous detachment (PVD) induction can be challenging in children. Do you typically use a stain-*

*ing agent or other instruments besides the vitreous cutter to lift the hyaloid?*

**AB:** I stain all these cases because I want to be completely sure that I've elevated the hyaloid. I generally start by trying to induce a PVD without kenalog, then inject the kenalog later for confirmation. In a 2-year old, the youngest child I have treated so far, the vitreous behaved more like the vitreous of a normal child. It was very adherent at the macula, so I used a flex loop to tease the vitreous away from the macula, then worked the PVD out more peripherally with the cutter.

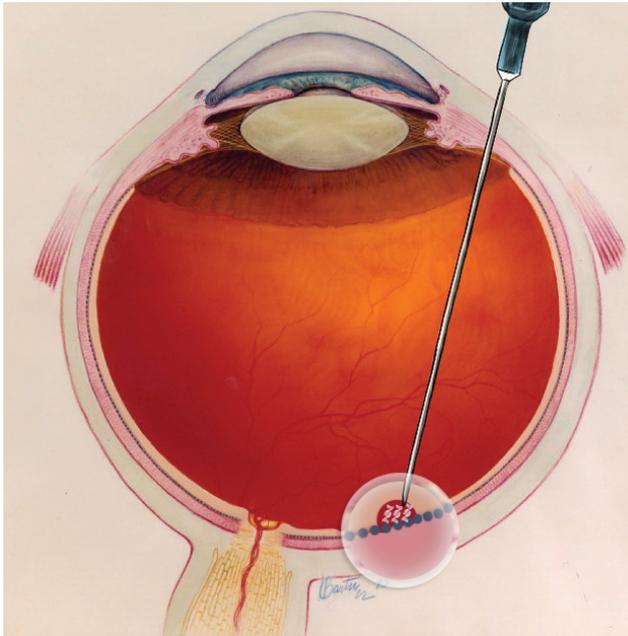
**NY:** *How aggressive are you in shaving the peripheral vitreous?*

**AB:** I try to elevate the hyaloid as far peripherally as possible, then I trim it with the cutter, but I don't typically do a 360-degree depressed shave. However, I do depress 360 degrees to look for any abnormalities or retinal breaks as I trim the vitreous. You don't want to have an unrecognized retinal break or detachment in these children. I would rather treat anything suspicious in the periphery with laser since I'm already in the eye. Thus far I

### Bios

Dr. Yannuzzi is a vitreoretinal surgery fellow at Bascom Palmer Eye Institute at the University of Miami Miller School of Medicine. Dr. Berrocal is director of pediatric retina at Bascom Palmer.

**DISCLOSURES:** Drs. Yannuzzi and Berrocal have no relevant financial relationships to disclose.



**Figure 1.** The tip of the microinjector needle is placed beneath the neural retina, where it injects the gene vector into a bleb above the retinal pigment epithelium layer.

*injector. What has been your experience?*

**AB:** I've tried using the injector non-beveled, but haven't been that successful in entering the subretinal space. Beveling it allows entry in a more elegant way.

### Usefulness of intraoperative OCT

*NY: Do you routinely use intraoperative optical coherence tomography*

*for these cases?*

**AB:** For these cases, intraoperative OCT is a must. It allows you to confirm the extent of the bleb (both vertically and horizontally), the location of the medication and whether the fovea has been detached. In the clinical trial, among children that were treated, there was one case of iatrogenic macular hole. By using the OCT, I can also confirm no hole has been induced.

*NY: How much volume do you inject and where do you typically aim to make your blebs?*

**AB:** You want to inject 0.3 ml, as was done in the clinical trial. Many times this can't be done in a single bleb. If the retina becomes too elevated or thin, it's possible to create a hole. As I perform the injection, I use OCT to get a feel for the height of the bleb. Ideally I start within the arcades to ensure some uptake in the macula. I will occasionally form two to four communicating blebs or non-communicating blebs.

### Macular and foveal detachment

*NY: Do you think macular and foveal detachment is necessary for success?*

**AB:** There are different schools of

have observed only one small retinal tuft in one eye and I treated it.

*NY: How is the vitreoretinal interface in these patients?*

**AB:** The younger the patient, the more normal the posterior adhesion is. Usually in the periphery the vitreous tends to be less adherent. Older children with more significant disease are easier to elevate.

### Using the microinjector

*NY: You did your first several cases by injecting manually with an assistant. Since then, you've transitioned to the MicroDose microinjector (MedOne). Do you find this to be a more controlled way of delivering the drug?*

**AB:** Definitely there's better control. The injection pressure is known, and you don't have the added variable of not knowing how hard the assistant is pushing. Too high of an injection pressure can cause trauma to the retina or retinal pigment epithelium. The MedOne micro-injector kit works great and it makes you an independent surgeon, which is always more controlled.

*NY: There are differences in opinions on whether to bevel the needle for the*

**For these cases, intraoperative OCT is a must. It allows you to confirm the extent of the bleb, the location of the medication, and whether the fovea has been detached.**

thought about this. The clinical trial required detachment at the macula. But what I've noticed is that you can get close to it and even if it doesn't occur completely, you can still have a good result. Sometimes, I'll lift two separate blebs that eventually communicate with each other at the macula.

**NY:** *What tamponade do you use for these cases?*

**AB:** The trial used an air-fluid exchange to eliminate the virus from the preretinal space and decrease inflammation. That's what I've been doing in all my cases.

### Steroid therapy

**NY:** *What steroids are you using pre-, intra- and postoperatively?*

**AB:** I prescribe 1 mg/kg per day of oral prednisone starting three days before the surgery and continue this until 10 days after the second eye. Ideally, I space each eye apart between seven and 18 days. I also give the child a sub-Tenon's kenalog injection at the end of surgery and topical steroids postoperatively. I've observed some moderate steroid responses, but all of my patients have been controlled on topical glaucoma agents, and their [intraocular] pressure normalized off medications after the steroids were tapered.

### Measuring success, recovery

**NY:** *In children, visual acuity and other objective outcome measures can be difficult to ascertain. How can you measure success in these cases?*

**AB:** Success is really seeing these kids need less light and less help and having surgery without complications. The clinical trial never used Snellen acuity as an endpoint. We're  
(Continued on page 31)



Figure 2. Audina Berrocal, MD, performing the operation to place the gene vector in the subretinal space. (Courtesy University of Miami Miller School of Medicine)

### A patient's mother's perspective on gene therapy

In this exchange, Nicolas Yannuzzi, MD, (NY) interviews a patient's mother (PM) about the child's experience with receiving the voretigene neparvovec vector.

**NY:** *Tell us about when you first learned your child's diagnosis. How did you determine something was wrong, and how was your child diagnosed?*

**PM:** The very first indicator was at our pediatrician's office for the one-year visit. The pediatrician used an automated visual screener, and my child didn't pass the test. The pediatrician suspected strabismus and referred us to an ophthalmologist. Then at 14 months old, he developed nystagmus. We came to Bascom Palmer to see Dr. [Craig] McKeown, who diagnosed a retinal dystrophy. ERG (electroretinogram) was recommended at that time, but I delayed it until my child was 1.5 years old.

During that time, I did a lot of research about dystrophies. I could tell he was night-blind, so I felt it was likely to be a rod-cone dystrophy. We then did a genetic test with a local ophthalmologist. I read articles on the American Academy of Ophthalmology website about a child who had been successfully treated by Dr. Berrocal, and that's how I ended up bringing my child to her.

**NY:** *How did you explain things to your child?*

**PM:** My child was 2 years old at the time. He was verbal and understood he needed extra light. I talked to him about fixing his eyes and putting medicine in them. We practiced using eye patches at home and watched some videos about it. I talked to him about other children who had experienced it and he felt more comfortable having seen others who had done it.

**NY:** *What changes have you noticed since treatment? When did they occur?*

**PM:** I noticed changes very rapidly the day we took the eye patch off. He was very light-sensitive. He started walking around the hotel more confidently and finding things on the floor in ambient light. We visited a Walmart and he felt it was a different store because it was so much brighter than before. He's gained a lot of confidence.

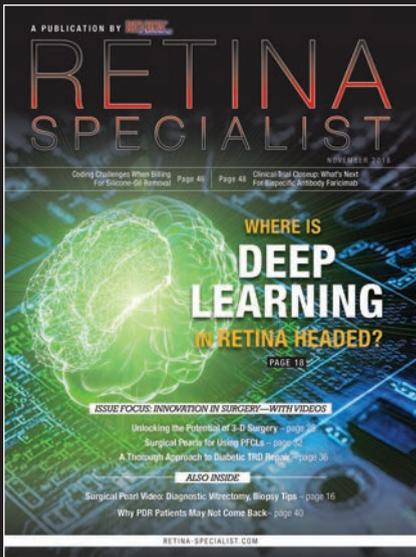
**NY:** *Is there anything you wish you had known prior to starting the process?*

**PM:** I would suggest doing the genetic testing early. Spark Therapeutics was also very supportive throughout the process. I would have worked with them earlier to help us to work with our insurance company.

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# Where steroids fit for DME in the anti-VEGF era

*The dexamethasone implant is an option for sustained release when treating macular edema, but DRCR.net Protocol U shows the limits of steroid use.*



Raj K. Maturi, MD

By Raj K. Maturi, MD

## Take-home points

- » Ozurdex in combination with ranibizumab achieved improvements in vision similar to ranibizumab alone.
- » However, the combination group showed significantly greater reduction in central subfield thickness.
- » Retina specialists must be mindful of significant intraocular pressure increases when treating with steroids.
- » Phakic patients have greater risk of cataract.

The overall results of Diabetic Retinopathy Clinical Research Network Protocol U,<sup>1</sup> a short-term study comparing the additive benefits of a dexamethasone implant (Ozurdex, Allergan) to ranibizumab (Lucentis, Roche/Genentech) in patients with persistent macular edema and visual loss, showed no visual benefit from the combination treatment.

The study only enrolled subjects with macular edema that persisted despite at least three monthly ranibizumab injections and at least three additional anti-VEGF injections prior to enrollment. Thus, subjects had to have residual macular edema with vision loss after a minimum of six injections of anti-VEGF.

The primary endpoint was the visual acuity gain after 24 weeks on combination or ranibizumab-alone treatment. Overall, the additional visual acuity gain was 3 letters in each group. Prior to this, subjects had already gained 3 letters when treated with ranibizumab Q4 weeks under the study protocol. Thus, there was no overall difference in acuity between the groups.

Here, I review the key findings of Protocol U and how they can enlighten our clinical approach to using the dexamethasone implant in our retina practices.

## Where did Protocol U show visual benefit?

On preplanned secondary analysis, we found a greater proportion of subjects with a 15-letter or greater improvement in vision in the combination group vs. the ranibizumab-only group (11 vs. 2 percent,  $p=0.03$ ). We also found that the combination group had a small increase in the proportion of patients with decreased vision over 10 letters (13 vs. 6 percent,  $p=0.09$ ), but this was not statistically significant.

## Where did Protocol U show anatomic benefit?

We found that central subfield thickness reduced significantly more in the combination group than in the ranibizumab-only group (110  $\mu\text{m}$  vs. 62  $\mu\text{m}$ ,  $p<0.001$ ). Additionally, about 50 percent of the combination group had a flat retina at week 24 compared with 31 percent of the ra-

## Bio

Dr. Maturi specializes in vitreoretinal medicine and surgery at Midwest Eye Institute, Indianapolis, and is a clinical associate professor, volunteer, at Indiana University School of Medicine.

**DISCLOSURES:** Dr. Maturi is on the executive committee of the Diabetic Retinopathy Clinical Research Network. He has received research funding from Kalvista Pharmaceuticals, Graybug Vision, Allergan, Genentech, Allegro Ophthalmics, Aerpio Pharmaceuticals, Jaeb Center for Health Research and Boehringer Ingelheim.

nibizumab-only group ( $p=0.02$ ). The improvement in OCT thickness was rapid and sustained in the combination group. This would be expected because Ozurdex was provided every 12 weeks, not every 24 weeks per the label indication. The investigators believe its duration of action is far shorter than what the label stipulates.

### What about pseudophakic patients?

The study was initially conceived to include pseudophakic subjects only. However, it was very difficult to recruit for the study, so we finally expanded it to include phakic subjects. We examined the pseudophakic subgroup and found that their visual acuity tracked that of the phakic subgroup's through week 20.

At the end of the study, the 24th week after randomization, the pseudophakic group had a 5-letter gain in acuity while the phakic group had a 2-letter gain, but this difference at this one time point did not reach significance. The study was not sufficiently powered to determine if pseudophakic patients would benefit from treatment early in the disease process. We just didn't have sufficient numbers for this analysis.

### What about intraocular pressure?

The entry criteria for the study were rather strict with regards to potential subjects not having any history of steroid responsiveness. For example, the study excluded subjects with any history of intraocular pressure risk with topical steroids in the fellow eye. Despite this careful exclusion, about 30 percent of the combination group had a significant rise in IOP, with 20 percent requiring treatment. It's possible that this pressure rise was more common than in the MEAD studies because the frequency of Ozurdex injection was higher (12- vs. 24-week interval).<sup>2</sup>

### Who might benefit from steroids?

The previous DRCR.net Protocol I study demonstrated that approximately 40 percent of patients treated with ranibizumab

continued to have macular edema after six months of treatment.<sup>3</sup> Of these, only 32 percent had visual acuity loss with macular edema. Protocol T, which compared aflibercept (Eylea, Regeneron), bevacizumab (Avastin, Roche/Genentech) and ranibizumab, showed that 16, 40 and 27 percent of subjects, respectively, had persistent edema with vision loss of at least 20/32 after six monthly injections.<sup>4</sup> These might be the patients most likely to benefit from alternative treatment options, including steroids and laser.

### Ozurdex in my practice

In my clinical practice, I use intraocular steroids, mostly Ozurdex, in select cases. I'm most likely to use this drug in patients who have persistent mild edema despite anti-VEGF and are scheduled for cataract surgery relatively soon. Pretreatment with Ozurdex seems to prevent worsening the macular edema that often occurs in this subgroup of patients. Otherwise, I believe there's a very limited role for steroids in phakic patients.

There may be a benefit to having a retina without edema rather than a retina that continues to have edema, even if measured Early Treatment Diabetic Retinopathy Study visual acuity is the same. The DRCR.net studies show that a patient can have stable and even improving vision in the presence of edema for at least two years. However, the patient may be missing some visual function, even if it's not measurable with high-contrast letters. For example, a patient's low-contrast acuity, which may reflect real-world night vision, may be limited in the presence of increased edema. We just don't know, because few studies have looked at such variables closely.

Despite the potential benefit of steroids for reducing edema—about 50 percent more than anti-VEGF alone—their side-

*(Continued on page 31)*



The Ozurdex implant, next to a dime for scale, and the applicator.

# Integrins' role in edema and how to disrupt it

*Integrin receptors play an important role in multiple pathological processes. Emerging drug candidates target the integrin pathway.*



David S. Boyer, MD

By David S. Boyer, MD

## Take-home points

- » Integrins play an important role in pathological processes that contribute to multiple ocular diseases.
- » Inhibition of integrins targets multiple processes involved in pathological angiogenesis and vascular leakage.
- » Targeting the integrin pathway could result in therapeutic effects that are both dependent on and independent of vascular endothelial growth factor.
- » Three drug candidates are targeting the integrin pathway: Risuteganib (Allegro Ophthalmics); SF0166 (SciFluor Life Sciences); and THR-687 (Oxurion).

Integrin receptors play an important role in multiple pathological processes associated with various eye diseases, including wet age-related macular degeneration and diabetic retinopathy. Increasing knowledge of the roles integrins play in ocular disease processes has generated interest in the integrin pathway as a therapeutic target. Three agents now in clinical trials are the focus of capitalizing on this knowledge.

This article describes the role integrins have in angiogenesis, inflammation and neovascularization, and discusses the clinical trials of the three investigational drugs targeting the integrin pathway.

## Integrins' structure and function

Integrins are transmembrane receptors that are heterodimers, which means they consist of both  $\alpha$  and  $\beta$  subunits. They mediate cell-to-cell and cell-to-extracellular interactions, the latter in the retinal matrix.<sup>1,2</sup> Integrins modulate cell signaling and are involved in various biological path-

ways. They've been implicated in various eye diseases, including cornea neovascularization; glaucoma and dry eye, along with both dry and wet AMD and diabetic retinopathy.<sup>3,4</sup>

There are four classes of integrin receptors, classified based on how they recognize integrin isoforms (*Figure*). They are:

- functional arginine-glycine-aspartic acid (RGD) integrin receptors;
- collagen integrin receptors;
- leukocyte-specific integrin receptors; and
- laminin integrin receptors.

They each play a different role in the four primary pathologic processes: angiogenesis;<sup>5-10</sup> permeability;<sup>10-14</sup> inflammation;<sup>10-13,15,16</sup> and fibrosis<sup>17-21</sup> (*Table, page 30*). Multiple RGD integrin receptors have been implicated in the disease processes of wet AMD and DR. For example, targeting specific subunits of RGD, collagen and integrin receptors would effectively target fibrosis, whereas angiogenesis is a function of specific RGD receptors.

## Bio

Dr. Boyer is principal partner at Retina-Vitreous Associates Medical Group in Los Angeles.

**DISCLOSURES:** Dr. Boyer is a consultant to Allegro Ophthalmics, SciFluor Life Sciences, Oxurion (formerly ThromboGenics), Genentech, Roche and Regeneron. He also has an ownership interest in Allegro.

## Risuteganib

Risuteganib (RSG) is a synthetic, RGD-class peptide that targets the retinal pigment epithelium and the outer retina. It has a molecular weight of 750 Dalton and a very long half-life of 21 days. It is designed to regulate three integrin isoforms identified in the pathological process:

- $\alpha V\beta 5$ , which signals angiopoietin-2 (Ang-2)-induced astrocyte apoptosis, contributing to vascular leakage in DR;
- $\alpha 5\beta 1$ , a contributor to the angiogenesis pathway that's different from vascular endothelial growth factor-mediated angiogenesis; and
- $\alpha M\beta 2$ , an isoform involved in inflammatory response.

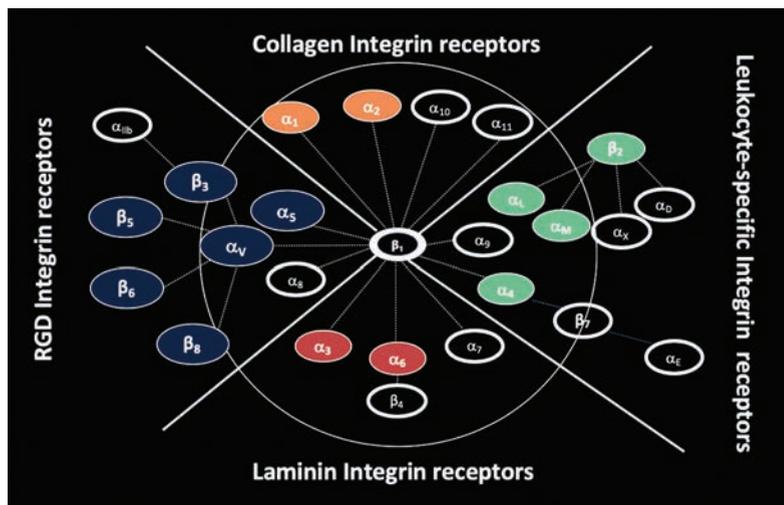
Julie Kornfield, PhD, at the California Institute of Technology, and Peter Campochiaro, MD, at Johns Hopkins University, have reported that RSG downregulates genes associated with five angiogenesis-related biological processes:

1. Integrin-mediated signaling pathway.
2. Tube development.
3. Extracellular matrix organization.
4. Circulatory system development.
5. Response to stimulus.

RSG has also been shown to reduce neovascularization in the ischemic retinopathy model. Additionally, Dr. Campochiaro and colleagues have reported that RSG reduced the total area of neovascularization by approximately 87 percent, vs. approximately a 50-percent reduction for aflibercept (Eylea, Regeneron).<sup>22</sup>

RSG has also been shown to downregulate gene expression in human immune cells, which have shown a proven immune and inflammatory response, and a response to stimuli. (These integrin receptors become activated only when an insult occurs; otherwise, they don't have any significant response.)

Glenn Jaffe, MD, and colleagues at Duke Eye Center reported on the protective effects of RSG in cultured human



**Figure.** This diagram shows the four classes of integrin receptors, based on how they recognize integrin isoforms. (Image courtesy Oxurion)

RPE cells.<sup>23</sup> Relative growth in cells treated with RSG was 34 percent vs. 18 percent in non-RSG cells; cell viability in terms of mitochondrial membrane potential was 79 percent vs. 46 percent; and 74 percent of cells with RSG exhibited cell viability vs. 42 percent of non-RSG cells.

### Findings of DEL MAR trial

The DEL MAR Phase II trial has demonstrated the efficacy and safety of RSG in patients with DME. The study reported that previously treated patients on RSG had more robust visual gains compared to treatment-naïve patients, and that a regimen of three monthly injections of RSG was non-inferior to monthly bevacizumab (Avastin, Genentech/Roche).

Stage one of the Phase II DEL MAR study evaluated patients on RSG 1 and 3 mg and bevacizumab 1.25 mg monthly for three months. The RSG 1-mg group had better overall results than the other RSG dosing groups. At 20 weeks, the previously treated patients on RSG 1 mg had a more robust response than the treatment-naïve patients, with a mean gain of 20 Early Treatment Diabetic Retinopathy Study letters vs. 11.

In DEL MAR stage 2, overall mean

**Risuteganib has been shown to reduce neovascularization in the ischemic retinopathy model.**

**Preclinical studies have shown SF0166 reduces VEGF-induced vascular leakage comparably to bevacizumab.**

change in ETDRS letters at 20 weeks was similar between the 1.25-mg bevacizumab-only group and the 1.25-mg bevacizumab/1-mg RSG combination group: 6.7 for the former and 7.1 for the latter.

This stage of the study also showed that the sequence of the drugs was important. Patients first given bevacizumab and then given three injections of RSG had a more profound response than those given the drugs simultaneously. This applied in both the previously treated (24-letter gain) and the treatment-naïve (17-letter gain) groups, with no improvement in the simultaneously dosed patients. The Phase II study of RSG for dry AMD is ongoing.

### Topical SF0166

SF0166 (SciFluor Life Sciences) is a selective, small-molecule inhibitor applied topically. It inhibits the RGD integrin receptor  $\alpha_V\beta_3$ , a non-fluorinated factor in angiogenesis. The fluorinated molecule structure of SF0166 enables it to penetrate the sclera and allows broad distribution of the drug. SF0166 has been found in high concentrations in the sclera and retina-choroid plexus for at least 12 hours after administration.<sup>24</sup>

Preclinical studies have shown SF0166 reduces VEGF-induced vascular leakage comparably to bevacizumab.<sup>25</sup> Results of a Phase I/II trial in patients with DME have so far shown no corneal toxicity or other drug-related serious adverse events. The study has also found measurable changes in central subfield thickness (CST) after treatment in both the 2.5% and 5% SF0166 treatment groups. At the end of treatment on day 28, 10 of 35 subjects showed decreases in CST, but at the end of the study on day 56, 19 of 38 subjects showed a decrease in CST. This illustrates a trend toward increased anatomic response from day 28 to day 56 of treatment. Of note: The trial has found no overall change in visual acuity and no correlation between CST and BCVA changes.

The safety profile coupled with evidence

## Pathological processes and integrin receptor classes implicated in them

### Angiogenesis<sup>5-10</sup>

- RGD:  $\alpha_V\beta_3$ ,  $\alpha_V\beta_5$ ,  $\alpha_V$ ,  $\alpha_5\beta_1$

### Permeability<sup>10-14</sup>

- RGD:  $\alpha_V\beta_3$ ,  $\alpha_V\beta_5$ ,  $\alpha_5\beta_1$
- Leukocyte:  $\alpha_4\beta_{1(-7)}$ ,  $\alpha_L\beta_2$ ,  $\beta_2$
- Laminin:  $\alpha_3\beta_1$

### Inflammation<sup>10-13,15,16</sup>

- RGD:  $\alpha_V\beta_3$ ,  $\alpha_V\beta_5$ ,  $\alpha_5\beta_1$
- Leukocyte:  $\alpha_4\beta_{1(-7)}$ ,  $\alpha_L\beta_2$ ,  $\alpha_M\beta_2$
- Laminin:  $\alpha_3\beta_1$

### Fibrosis<sup>17-21</sup>

- RGD:  $\alpha_V\beta_3$ ,  $\alpha_V\beta_5$ ,  $\alpha_V\beta_6$ ,  $\alpha_5\beta_1$
- Collagen:  $\alpha_2\beta_1$ ,  $\alpha_1\beta_1$
- Laminin:  $\alpha_6\beta_1$ ,  $\alpha_3\beta_1$

of biological activity warrants further study of SF0166 in Phase II trials investigating expansion of the dose range, as well as treatment and follow-up periods.

### THR-687

THR-687 (Oxurion) is a highly potent, small-molecule pan-RGD integrin antagonist. In preclinical study, it has been shown to inhibit endothelial cell migration, which is involved in angiogenesis.<sup>26</sup> Extensive toxicology and safety pharmacology studies indicate a good safety profile for this drug. It has broad therapeutic potential for treating DR with or without DME, wet AMD and anti-VEGF nonresponders. The first patient in a Phase I trial for treatment of DME has been enrolled. <sup>RS</sup>

## REFERENCES

1. Berrier AL, Yamada KM. Cell-matrix adhesion. *J Cell Physiol*. 2007; 213: 565-573.
2. Ruoslahti E. RGD and other recognition sequences for integrins. *Annu Rev Cell Dev Biol*. 1996;12:697-715.
3. Gonzalez-Salinas R, Hernández-Zimbrón LF, Gullias-Cañizo R, et al. Current anti-integrin therapy for ocular disease. *Semin Ophthalmol*. 2018;33:634-642.
4. Goswami LN, Ma L, Cai Q, et al. cRGD peptide-conjugated icosahedral closo-B12(2-) core carrying multiple Gd3+-DOTA chelates for (v)3 integrin-targeted tumor imaging (MRI). *Inorg Chem*. 2013 18;52:1701-1709.
5. Friedlander M, Theesfeld CL, Sugita M, et al. Involvement of integrins alpha v beta 3 and alpha v beta 5 in ocular neovascular diseases. *Proc Natl Acad Sci U S A*. 1996;93:9764-9769.
6. Umeda N, Kachi S, Akiyama H, et al. Suppression and regression of choroidal neovascularization by systemic administration of

an alpha5beta1 integrin antagonist. *Mol Pharmacol*. 2006;69:1820-1828.

7. Wilkinson-Berka JL, Jones D, Taylor G, et al. SB-267268, a nonpeptidic antagonist of alpha(v)beta3 and alpha(v)beta5 integrins, reduces angiogenesis and VEGF expression in a mouse model of retinopathy of prematurity. *Invest Ophthalmol Vis Sci*. 2006 Apr;47:1600-1605.

8. Fu Y, Ponce ML, Thill M, Yuan P, Wang NS, Csaky KG. Angiogenesis inhibition and choroidal neovascularization suppression by sustained delivery of an integrin antagonist, EMD478761. *Invest Ophthalmol Vis Sci*. 2007;48:5184-5190.

9. Hammes HP, Weiss A, Führer D, Krämer HJ, Papavasiliou C, Grimminger F. Acceleration of experimental diabetic retinopathy in the rat by omega-3 fatty acids. *Diabetologia*. 1996;39:251-255

10. Santulli RJ, Kinney WA, Ghosh S, et al. Studies with an orally bioavailable alpha V integrin antagonist in animal models of ocular vasculopathy: retinal neovascularization in mice and retinal vascular permeability in diabetic rats. *J Pharmacol Exp Ther*. 2008;324:894-901

11. Joussen AM, Poulaki V, Le ML, et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. *FASEB J*. 2004;18:1450-2.

12. Iliaki E, Poulaki V, Mitsiades N, Mitsiades CS, Miller JW, Gragoudas ES. Role of alpha 4 integrin (CD49d) in the pathogenesis of diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2009;50:4898-4904.

13. Rao Malla R, Gopinath S, Alapati K, Gorantla B, Gondi CS, Rao JS. Knockdown of cathepsin B and uPAR inhibits CD151 and 3 1 integrin-mediated cell adhesion and invasion in glioma. *Mol Carcinog*. 2013;52:777-790.

14. Park SW, Yun JH, Kim JH, Kim KW, Cho CH, Kim JH. Angiopoietin 2 induces pericyte apoptosis via 3 1 integrin signaling in diabetic retinopathy. *Diabetes*. 2014;63:3057-3068.

15. Kanda A, Noda K, Oike Y, Ishida S. Angiopoietin-like protein 2 mediates endotoxin-induced acute inflammation in the eye. *Lab Invest*. 2012;92:1553-163.

16. Hirasawa M, Takubo K, Osada H, et al. Angiopoietin-like protein 2 is a multistep regulator of inflammatory neovascularization in a murine model of age-related macular degeneration. *J Biol Chem*. 2016;291:7373-7785.

17. Robbins SG, Brem RB, Wilson DJ, et al. Immunolocalization of integrins in proliferative retinal membranes. *Invest Ophthalmol Vis Sci*. 1994;35:3475-3485.

18. Ning A, Cui J, Maberley D, Ma P, Matsubara J. Expression of integrins in human proliferative diabetic retinopathy membranes. *Can J Ophthalmol*. 2008;43:683-688.

19. Zahn G, Volk K, Lewis GP, et al. Assessment of the integrin alpha5beta1 antagonist JSM6427 in proliferative vitreoretinopathy using in vitro assays and a rabbit model of retinal detachment. *Invest Ophthalmol Vis Sci*. 2010;51:1028-35.

20. Blanco-Mezquita JT, Hutcheon AE, Stepp MA, Zieske JD. V 6 integrin promotes corneal wound healing. *Invest Ophthalmol Vis Sci*. 2011;52:8505-8513.

21. Wang S, Park JK, Duh EJ. Novel targets against retinal angiogenesis in diabetic retinopathy. *Curr Diab Rep*. 2012;12:355-363.

22. Silva RLE, Kanan Y, Campochiaro PA, et al. Tyrosine kinase blocking collagen IV-derived peptide suppresses ocular neovascularization and vascular leakage. *Sci Transl Med*. 2017;9 pii: eaai8030

23. Yang P, Baciu P, Jaffe GJ, et al. Retinal pigment epithelial cell death by the alternative complement cascade: Role of membrane regulatory proteins, calcium, PKC, and oxidative stress. *Invest Ophthalmol Vis Sci*. 2014;55:3012-3021.

24. Press release SciFluor Life Sciences. SciFluor announces positive results of Phase I/II study of SF0166 topical ophthalmic solution in diabetic macular edema patients. Cambridge, MA: September 28, 2017.

25. SciFluor Life Sciences. Data on file.

26. Shao Z, Friedlander M, Hurst CG, et al. Choroid sprouting assay: an ex vivo model of microvascular angiogenesis. *PLoS One*. 2013;8:e69552.

## A real-world experience administering gene therapy

(Continued from page 24)

looking more at function. Doing visual fields in kids is impossible. We hope to do electroretinograms at follow-up visits. Contrast sensitivity is important, but it's very challenging to test a 2-year-old in the clinic.

**NY: What have you noticed about these children during recovery?**

**AB:** Three days after you inject the vector, parents already notice a change in the amount of light their children need. Imagine that three days after you inject the viral vector, retinal cell biology is changing. That to me is magic. It's almost like science fiction. As the weeks go by, parents send me videos and tell me about the amount of change they notice in the lives of their children.

**NY: What do you think about visual development in these children?**

**AB:** Studies have shown there's a lot of neural plasticity after the viral injection in these children. Patching is a must. I work with pediatric ophthalmologists for visual rehabilitation, and all of my colleagues have been attempting patching. Remember, many of these children haven't been tested visually for years or have not had amblyopia management because of their underlying disease.

**NY: Any other tips for these cases?**

**AB:** Although I use a noncontact system, I like a contact lens for the subretinal injection to enhance stereopsis. I suture the sclerotomies at the end of every case and give 20 mg of a sub-Tenon's kenalog. <sup>RS</sup>

## Where steroids fit for DME in the anti-VEGF era

(Continued from page 27)

effect profile makes them a less-desirable choice. In phakic patients, the risk of cataracts is sufficiently high that I wouldn't use steroids.

However, pseudophakic patients, especially those who are not steroid-responsive, may benefit from having a flat retina with the same ETDRS measured acuity vs. treatment with anti-VEGF alone. Other studies have shown comparable benefit when using steroids with anti-VEGF vs. steroids alone. This may also limit treatment and cost burden.

However, before choosing this approach, it's best to confirm the underlying diabetic retinopathy is well-controlled because I believe steroids don't regress diabetic retinopathy as well as anti-VEGF agents. Also, while Ozurdex may require treatment only every 12 weeks, many patients will require IOP monitoring every four to eight weeks.

### Bottom line

Definite anatomic benefits exist when adding Ozurdex to ranibizumab in DME, as studied in Protocol U. However, the benefits of steroids are limited by their side-effect profile. In Protocol U, overall acuity was similar in both study groups, confirming the limits of steroid use. <sup>RS</sup>

### REFERENCES

- Maturi RK, Glassman AR, Liu D, et al, for the Diabetic Retinopathy Clinical Research Network. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: A DRCR Network Phase 2 randomized clinical trial. *JAMA Ophthalmol*. 2018;136:29-38.
- Maturi RK, Pollack A, Uy HS, et al; Ozurdex MEAD Study Group. Intraocular pressure in patients with diabetic macular edema treated with dexamethasone intravitreal implant in the 3-year MEAD study. *Retina*. 2016;36:1143-1152.
- Gonzalez VH, Campbell J, Holekamp NM, K. Early and long-term responses to anti-basilar endothelial growth factor therapy in diabetic macular edema: Analysis of Protocol I data. *Am J Ophthalmol*. 2016;172:72-79.
- Cai S, Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: Recent clinically relevant findings from DRCR.net Protocol T. *Curr Opin Ophthalmol*. 2017;28:636-643.

# PIVOT authors' pneumatic retinopexy tips

*These insights can help achieve successful outcomes when repairing rhegmatogenous retinal detachments.*

**By Rajeev H. Muni MD, MSc, FRCSC, and Roxane J. Hillier, BSc, MBChB, FRCOphth, MSc**



**Department Editor  
Efrem D. Mandelcorn, MD, FRCSC**

## Bios

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

Dr. Muni is a vitreoretinal surgeon at St. Michael's Hospital and vice chairman, clinical research in the department of ophthalmology and vision sciences at the University of Toronto.

Dr. Hillier is consultant ophthalmologist and vitreoretinal surgeon at Newcastle Eye Centre, Royal Victoria Infirmary in Newcastle, U.K., and associate clinical lecturer at the Institute of Neuroscience, Newcastle University.

**P**neumatic retinopexy involves injection of a gas bubble into the vitreous cavity and application of retinopexy to causative retinal breaks. In the last issue, we discussed in this space the rationale, design and findings of the PIVOT study, a randomized controlled trial that compared pneumatic retinopexy and pars plana vitrectomy.<sup>1</sup> Here, we provide some tips and tricks that may help optimize anatomical re-attachment rates when performing pneumatic retinopexy.

## Steps before pneumatic retinopexy

Prior to injecting the gas in pneumatic retinopexy, it's essential to carefully examine the peripheral retina with indirect ophthalmoscopy and 360-degree scleral indentation to visualize all pathology. We recommend pretreating any lattice degeneration or breaks in attached retina with laser retinopexy because this offers swift adhesion compared to cryopexy.

In cases with small peripheral breaks in the detached retina, which may be difficult to visualize after gas injection, cryopexy before pneumatic retinopexy can be helpful. This step may aid in operating on aphakic patients or those with anterior chamber/iris clip lenses that make break visualization onerous through gas.

In some cases we've found that marking the edge of the retinal break itself with laser (a challenging task in its own right) or, alternatively, marking the ora serrata in the meridian of the retinal break will assist with identification and treatment of the break with laser retinopexy once the retina has reattached.<sup>2</sup>

## Optimizing the tamponade

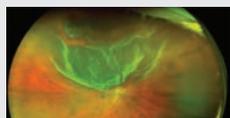
It's crucial to maximize the size of the injected gas bubble. We believe this is an important factor in determining the likelihood of anatomical success. The ideal gas for use in pneumatic retinopexy will expand quickly to facilitate prompt retinal reattachment and laser, followed by quick resorption. We prefer pure SF-6 gas because it expands over 48 hours and lasts 12 days.

We recommend injecting 0.3 cc of pure SF-6 greater than the anterior chamber tap volume, and rarely less than 0.6 cc. For example, if 0.8 cc can be removed from the anterior chamber, then 1.1 cc of pure SF-6 gas can be injected. In order to maximize the volume of the anterior chamber tap, we like to perform the procedure with the patient supine.

A 30-gauge needle on a 1-cc syringe with the plunger removed is inserted temporarily, and is passed obliquely over the iris in phakic patients and radially in pseudophakes. We place the plunger behind the limbus opposite the needle entry site to create a dome over the needle tip. Applying constant and firm pressure with the plunger encourages expression of aqueous and liquefied vitreous.

## When a larger gas bubble is needed

In cases that require a gas bubble that's larger than what can be injected in a single sitting, we recommend sequential gas bubble injections. This is preplanned in some cases, and done emergently in others depending on how the case evolves. In both scenarios, sequential gas bubble



## View the Video

Drs. Muni and Hillier demonstrate the pneumatic retinopexy technique as performed in the PIVOT trial. Available at: [http://bit.ly/RetSpec-Mag\\_05201901](http://bit.ly/RetSpec-Mag_05201901)

**Wide-field retinal images demonstrate outcomes of a phakic patient meeting PIVOT criteria. With a superior macula-off retinal detachment (A), the patient underwent laser retinopexy for inferior lattice pre-pneumatic retinopexy. At two hours post-pneumatic retinopexy with patient positioning face down, significantly less fluid is seen and some fluid is displaced nasally (B). At 15 hours post-pneumatic retinopexy, the retina is fully attached with coalesced bubbles (C). The patient underwent laser for a superior break 48 hours post-pneumatic retinopexy, demonstrating fully attached retina and superior break lasered (D). At 10 days post-pneumatic retinopexy, following reabsorption of the gas bubble (E), the retina is fully attached with all pathology lasered.**

injection has helped to increase retinal reattachment rates with pneumatic retinopexy.

When injecting the gas bubble, it's ideal to minimize the occurrence of “fish eggs” and achieve a single large bubble. We use a 3-cc syringe with a 30-ga. needle for gas injection, selecting an injection site at the highest point of the globe. The superotemporal quadrant is ideal, unless a gaping break at that location presents a risk of subretinal gas passage.

To inject the gas bubble, we advance the needle into the vitreous cavity approximately half of the way in, and then pull back so the tip is barely in. We then inject the gas in a steady and swift manner. This allows it to be injected into a single expanding bubble.

After the injection, we examine the posterior segment to assess for central retinal artery perfusion and perform an additional AC tap if the artery is occluded. If the artery is pulsatile, the surgeon can safely wait for a few minutes to see if it becomes non-pulsatile. If the patient is unduly uncomfortable, then a repeat AC tap is advisable.

### Post-injection steps

Diligent postoperative positioning is critical for success with pneumatic retinopexy. Patients are generally advised to position face down for four hours in macula-on cases and for six hours in macula-off cases to protect or preferentially reattach the macula, then slowly steamroll to the final desired position. For ex-

ample, in a superior bullous detachment, the patient would raise her or his head by 30 degrees every hour until reaching the head elevated position.

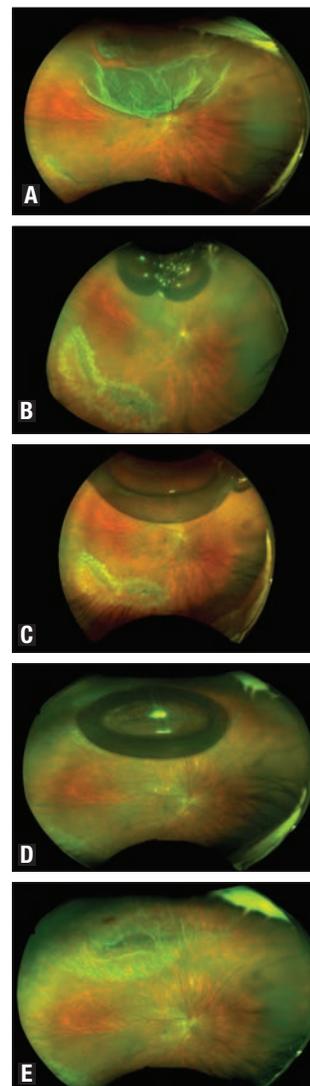
We advise patients to maintain the desired position for one week. In cases with inferior breaks in the attached retina, steamrolling is performed in a specific manner to encourage subretinal fluid to displace away from the inferior break. For an inferotemporal break in the attached retina, steamrolling with a left head tilt will encourage displacement of fluid superiorly and away from the inferior break.

We believe that one intrinsic advantage of pneumatic retinopexy is that it induces the retinal pigment endothelial “pump” to resorb the subretinal fluid naturally rather than using forced drainage as with pars plana vitrectomy. In many cases, once the gas bubble fully covers the retinal break, the subretinal fluid can resorb rapidly within hours (*Figure, at right*).

### Days later, indirect laser retinopexy

In the days following the pneumatic retinopexy, indirect laser retinopexy is applied around the retinal break and sometimes to adjacent areas that are suspicious. We encourage generous laser retinopexy. However, take care not to apply excessively heavy laser to areas where subretinal fluid remains.

Subconjunctival anesthesia can assist in performing laser retinopexy after  
(Continued on page 35)



### Disclosures

The authors have no relevant financial relationships to disclose.

# Striving for one-time AMD treatment

*HMR59 is an intravitreally administered gene therapy that has shown promise in disrupting the complement cascade.*

By **Richard Mark Kirkner**



**Department Editor  
Emmett T.  
Cunningham Jr.,  
MD, PhD**

**HMR59 is a gene therapy that infects retinal ganglion cells and results in production of a soluble protein called CD59 (sCD59).**

**H**MR59 (Hemera Biosciences) is a one-time gene therapy treatment that's being evaluated in clinical trials for treatment of both wet and dry age-related macular degeneration. HMR59 is administered intravitreally in the retina specialist's office, avoiding the need for subretinal placement of the gene vector in an operating room procedure.

HMR59 therapy infects retinal ganglion cells and results in production of a soluble protein called CD59 (sCD59) to block the final step of the complement cascade that causes some of the deleterious effects of macular degeneration. The clinical trials—HMR-1001,<sup>1</sup> a Phase I trial of 17 patients with dry AMD and geographic atrophy, and HMR-1002,<sup>2</sup> a Phase I study of 25 patients with newly diagnosed wet AMD that's treatment-naïve in the affected eye—have shown the drug is safe and has some clinical benefit.

Here, Elias Reichel, MD, professor and vice chair of ophthalmology at Tufts University School of Medicine in Boston, answers questions about HRM59. Dr. Reichel is founder and equity owner of Hemera Biosciences.

## The mechanism of action of HMR59 in his own words

HMR59 expresses a soluble version of CD59. Typically, CD59 is membrane-bound and it blocks complement factor 9 (C9) from attaching to the cell to form membrane attack complex (MAC), which is the final step in the complement cascade. MAC causes formation of a pore on the cell that leads to cell death.

Genetic research has shown an association between mutations and polymorphisms of genes in the complement cascade, and has implicated MAC in AMD. A person with a high-risk form of AMD

that's related to complement mutations has more MAC on autopsy tissue than normals. CD59 prevents C9 from entering the cell and completing the final step of MAC formation.

Interestingly, in Japan there have been reports of individuals who have insufficient levels of C9 and they have a reduced risk of developing wet AMD.

**Q What are the key findings of HMR-1001, the Phase I dose-escalation trial of HMR59 in dry AMD?**

**A** One-year data have shown about a 25-percent reduction in the growth rate of geographic atrophy. We've seen no conversions to wet AMD in these eyes, although we would expect 4 to 5 percent of eyes to develop choroidal neovascularization. Mild inflammation has been reported about 15 percent of the time in the trial. The inflammation either resolved on its own or responded to topical corticosteroids.

**Q How about HMR-1002, the Phase I trial in wet AMD?**

**A** This trial has recruited 15 patients. These patients received an intravitreal anti-VEGF injection at day zero and then the highest dose of HMR59, (3.56 x 10e11vg), one week later. During the first three months of follow-up, only about 15 percent of the time was there a need for a rescue injection of anti-VEGF.

**Q What's the potential explanation of why HMR59 may treat both wet and dry forms of AMD?**

**A** Strong scientific evidence supports the hypothesis that there are both lytic and sublytic levels of MAC that cause these different disease types. Higher lytic levels cause cell death of the retinal pigment epithelium, the chorio-

capillaris and, potentially, photoreceptors; that would lead to dry AMD or geographic atrophy.

Sublytic levels of MAC result in upregulation of vascular endothelial growth factor, which induces choroidal neovascularization. In wet AMD, we've seen a reduction in the need for anti-VEGF probably because HMR59 damps down the MAC.

**Q How does HMR59 differ from or complement existing treatments for AMD?**

**A** Other trials are investigating monthly intravitreal injections to treat geographic atrophy and ways of inhibiting other steps in the complement cascade. HMR59 is intended to be a one-time, in-office, intravitreal injection. The goal is for the treatment to hopefully modify the disease for the patient's lifetime.

The virus actually infects the ganglion cells. The gene therapy occurs in the cell nucleus with production of mRNA, which starts producing the soluble CD59. Because it is soluble, CD59 can be secreted from the cell and penetrate the retina.

**Q Potentially, where would HMR59 fit in the retina specialist's toolbox?**

**A** It's potentially useful for treatment of geographic atrophy and wet AMD, but we may be able to initiate earlier treatment when patients have intermediate drusen or atrophy that hasn't progressed to severe vision loss. This may be almost like a vaccine where the patient receives a treatment that prevents him from progressing from a very early stage of high-risk AMD.

**Q What are the next steps in the development?**

**A** For the dry-AMD study, 18-month data will be available soon. The wet-AMD study can enroll up to 25 patients (15 have been enrolled so far). Six-month data from the first dozen patients in the wet AMD trial may be very significant in showing the same reduction in treatment burden as they have in the first three months. <sup>RS</sup>

**REFERENCES**

1. Treatment of advanced dry age related macular degeneration with AAVCAGsCD59. ClinicalTrials.gov identifier NCT03144999. <https://clinicaltrials.gov/ct2/show/NCT03144999?term=NCT03144999&rank=1>. Accessed May 13, 2019.
2. AAVCAGsCD59 for the treatment of wet AMD. ClinicalTrials.gov identifier NCT03585556. <https://www.youtube.com/watch?v=e44VRsNJaHY&feature=youtu.be>. Accessed May 13, 2019.

**PIVOT authors' tips for pneumatic retinopexy**

*(Continued from page 33)*

pneumatic retinopexy in certain cases. Laser retinopexy can be challenging with a gas bubble present. Modifying the head position during the laser procedure helps to provide a view fully through the gas bubble or to divert the gas out of the way. In pseudophakes, having patients look straight up to the ceiling can provide a panoramic view of the retina, facilitating easier laser application.

**Determining success or failure**

Part of the art of pneumatic retinopexy is determining success or failure as the retina reattaches. Early on in one's experience with the procedure, there can be a tendency to abandon it prematurely and schedule surgery. One such scenario might be a case with residual inferior fluid, with the offending retinal tear attached and treated. In this case, proceeding to PPV can be problematic, as the inferior fluid would require creating an inferior retinotomy. In this situation, it's critical to assess the subretinal fluid that remains and determine if it's getting better or worse.

Search for any open untreated breaks. If the fluid has improved from baseline and has stabilized, then waiting for resorption is preferable. In some cases that can take weeks or months.

On the other hand, it's important to recognize when the procedure has failed. In the setting of a failed pneumatic retinopexy, undue delay to surgery could lead to worse outcomes. If secondary surgery is performed expeditiously, as several randomized trials have demonstrated, a failed pneumatic retinopexy doesn't jeopardize final re-attachment rates or visual outcomes.

**Bottom Line**

Although each step of a pneumatic retinopexy is seemingly simple, it's an art that can be acquired only with experience. Over time, you'll learn nuances and modifications that will allow you to perform the procedure successfully in a broad range of cases. Although the PIVOT criteria apply to a specific subset of retinal detachments, pneumatic retinopexy can be used in a wide variety of retinal detachment configurations. <sup>RS</sup>

**REFERENCES**

1. Hillier RJ, Felfeli T, Berger AR, et al. The Pneumatic Retinopexy vs. Vitrectomy for the management of Primary Rhegmatogenous Retinal Detachment Outcomes Randomized Trial (PIVOT). *Ophthalmology*. 2019;126:531-539.
2. Yan P, Minaker S, Mandelcorn ED. Laser marking of the meridian of retinal breaks at the ora: A novel technique for pneumatic retinopexy. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47:570-572.

# Checking your online reputation

*A review of social media platforms and physician-ratings site for retina specialists.*



**Department Editor**  
**David R.P. Almeida,**  
**MD, MBA, PhD**

**D**o you know what your online reputation is? In developing an online brand, as I discussed in the previous column, and getting into specific strategies for practice promotion via social media, you need to monitor your online presence. To do that, it helps to understand the basic platforms and relevant sources. So here I'll review the major social media platforms (Twitter, Facebook, LinkedIn, Doximity) and online physician ratings sites (Google, RateMDs.com, HealthGrades.com, Yelp). These platforms will help to distribute your brand to the population you serve.

## Online and social media basics

Social media platforms work best with an excellent practice website. The practice website must serve as a central source of information ranging from useful patient resources to a facile method of contacting the office and booking an appointment.

Moving beyond the practice website, Facebook is the largest social networking site with more than 2 billion monthly active users. Here, users can post comments, share photographs and post links. It allows text, short videos and live chats. Recently, Facebook has been battered because of privacy concerns and for allowing dissemination of false information. Because of this, I recommend you keep your practice or professional Facebook accounts separate from your personal page. This is essential to ensure the content posted and commented on your practice website remains of value to patients and colleagues.

Twitter, another online news and social networking site, differs in that people communicate in short messages or "tweets" of 280 characters or less. Currently, Twitter has about 300 million monthly active users. Twitter has two ma-

ior advantages: First, by limiting messages to 280 characters, content is easily generated and digested. Second, anyone can view your Twitter page even if they don't have a Twitter account themselves (although they will need an account to comment and share posts).

LinkedIn is a business-focused social networking site designed for professionals looking for new opportunities to grow their careers and connect with others. It is the online equivalent of going to a traditional networking event where you exchange business cards. LinkedIn currently has about 500 million active users on its platform.

Instagram, with 800 million active users, is a social networking application made for sharing photos and videos from a smartphone. It's very similar to Facebook and Twitter, but with a heavy emphasis on visual information (mostly photos and videos).

Finally, Doximity is a more specialized online social networking service specifically for U.S. clinicians. This social networking site has a variety of functions including contacts, a professional profile page, continuing medical education, ability to email, fax, or text colleagues, a medical news portal and a digital doctors lounge for conversation. Currently, about one in four U.S. physicians have a profile on Doximity and the site has more than 1 million verified users.

## Physician online rating sites

In addition to social media platforms, you need to be aware of online physician-rating sites. A 2016 Pew Research Center study found that 84 percent of U.S. adults use online ratings sites to inform their product or service-purchase decisions.<sup>1</sup>

Not surprisingly, health care is no  
*(Continued on page 38)*

### Bio

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**DISCLOSURE:** Dr. Almeida no relevant financial relationships.

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# Is laser for vitreous floaters covered?

Answers to one of the most common questions our coding expert gets.



**Department Editor**  
**Kirk A. Mack,**  
**COMT, COE,**  
**CPC, CPMA**

**L**aser therapy of vitreous floaters was not a topic that I was planning for this issue. However, we continue to get questions about YAG laser for vitreous floaters from both retina specialists and even general ophthalmologists. They ask about coding, coverage and reimbursement. I'll review those areas here. Note that vitrectomy for vitreous floaters, while coded differently, isn't part of this discussion, but much of the medical necessity discussion is germane.

## Coverage

The question is, "Is this covered by insurance?" Unfortunately, the answer is not so black and white. First, is the procedure medically necessary? In other words, is the floater(s) so significant that it limits vision and/or impedes a person's ability to perform a function or task? Sometimes the impact is significant, but one article states, "Vitreous opacities are almost universal, and most need no treatment."<sup>1</sup>

Consider medical necessity for treating a vitreous floater similar to when a surgeon documents medical necessity for cataract surgery. The surgeon documents how the cataract impacts or impedes activities of daily living (ADLs) and that there's a high likelihood that removing the cataract will improve or restore those ADLs. We recommend our clients use a questionnaire to score the severity of the floaters and document specific compromised ADLs. A sample questionnaire can be found at [www.corcoranccg.com/products/forms/laser-floater-ellex/](http://www.corcoranccg.com/products/forms/laser-floater-ellex/).

Government and commercial payers have published limited-coverage policies, but there are no published policies from any Medicare Administrative Contractors (MAC). We did find two commercial policies that consider this service non-covered.

Aetna's medical policy, YAG Laser in Ophthalmology and Other Selected Indications, states: "Aetna considers Nd: YAG laser vit-

reolysis experimental and investigational for the treatment of vitreous degeneration and vitreous floaters because its effectiveness for these indications has not been established."<sup>2</sup>

Florida Blue's position statement in its laser vitreolysis coverage guideline states: "Laser vitreolysis is considered experimental or investigational, for treatment of all other indications, and specifically vitreous floaters of the eye, as there is insufficient clinical evidence in the published peer-reviewed literature to support effectiveness."<sup>3</sup>

## Two codes to consider

Like the coverage, the coding isn't black and white. There are two codes to consider:<sup>4</sup>

- **67031**—Severing of vitreous strands, vitreous face adhesions, sheets, membranes or opacities, laser surgery, one or more stages.
- **67299**—Unlisted procedure, posterior segment.

The preference, when filing a claim, is 67031 and avoiding the unlisted code. When a floater is severed and sinks to the bottom of the vitreous and out of the line of sight, CPT 67031 likely applies. In contrast, if the floater is "vaporized," "destroyed" or fragmented into smaller pieces, the unlisted code, CPT 67299, would apply. *Severing* is the key term, defined in *Merriam-Webster Dictionary* as "to remove (something, such as a part) by or as if by cutting." CPT contains instructions to use an unlisted code when a specific code is unavailable.

If you use CPT 67031, don't overlook the "one or more stages" designation. This means the surgeon gets one payment for the procedure even if the same laser treatment is repeated during the postoperative period.

## Utilization and reimbursement

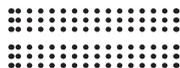
Within Medicare, these procedures are not performed often. According to the 2017 Medicare paid claims data, CPT 67031 was



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## Bio

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reimbursed 5,815 times while CPT 67299 was reimbursed 160 times. The 2019 national Medicare Physician Fee Schedule reimbursement rate for 67031 is \$400 in the office and \$380 in an outside facility. Relative Value Units (RVUs) aren't assigned to the unlisted code, 67299, so surgeon reimbursement is determined on a case-by-case basis.

### Bottom line

It's important to consider the medical necessity for laser treatment of vitreous floaters. Without significant symptoms and/or an impact on function, it probably won't be covered. Ultimately, it's the physician's decision to treat the problem, but if the patient insists and medical necessity is lacking, consider using an advanced beneficiary notice of coverage (ABN) or similar waiver for non-Medicare patients. In those cases, the patient is financially responsible for the service. In the same way, if the unlisted code (67299) is used, initiating an ABN or waiver is a good idea because payers often determine coverage for unlisted services after reviewing supporting documentation.

To avoid any coverage dilemmas with patients who have floaters, develop a process to evaluate and document medical necessity and create an ABN or waiver to inform the patients of any financial obligations. Finally, watch the subtle language in the codes; it's very likely that 67299 will be used for many of these procedures. <sup>RS</sup>

### REFERENCES

1. Karickhoff JR. YAG Laser offers safe option for floaters. *Ocular Surgery News*. <https://www.healio.com/ophthalmology/retina-vitreous/news/print/ocular-surgery-news/%7Be3262a47-4d0d-4231-8613-6d225ab1c4bc%7D/yag-laser-offers-safe-option-for-floaters> Updated March 15, 2007. Accessed May 6, 2019.
2. Aetna. Policy Number: 0354. YAG Laser in Ophthalmology: Selected Indications. Last reviewed 04/10/2019. [http://www.aetna.com/cpb/medical/data/300\\_399/0354.html#dummyLink1](http://www.aetna.com/cpb/medical/data/300_399/0354.html#dummyLink1). Accessed April 14, 2019.
3. Blue Cross/Blue Shield of Florida. Medical Coverage Guidelines: Laser vitreolysis. Revised May 11, 2014. <http://mcgs.bcbssf.com/>

### Check your online reputation (Continued from page 36)

different. A 2017 National Institutes of Health study found 53 percent of physicians and 39 percent of patients reported visiting a health care rating website at least once to evaluate a physician or practice.<sup>2</sup>

The main physician and health-care ratings sites include Google (widespread, with major impact from practice and personal websites affecting internet visibility); RateMDs.com (2.6 million reviews); HealthGrades.com (6.1 million reviews); Vitals.com (7.8 million reviews); and Yelp (more commonly used for ratings of hospitals and larger health-care organizations). Unfortunately, anyone can post to these sites and verification remains a problem. Still, we must accept this; it's unlikely to change.

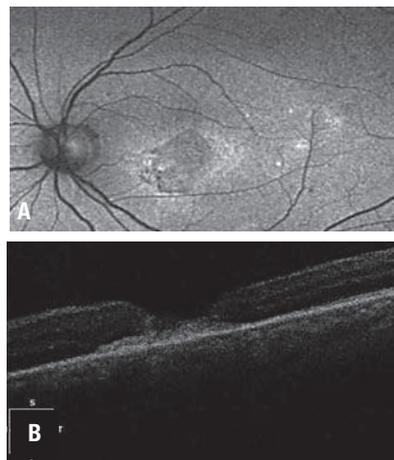
Are you aware of the patient reviews and health grades you've received? Are there any negative reviews or pages if you Google your name or your practice? Monitoring your online presence is crucial and, if any negative reviews exist, you must address them because they won't disappear.

Now that you understand the importance of branding and are aware of social media platforms and online ratings sites, you're ready to increase your presence as part of an online strategy. The next question is, where do you start? Next time, we'll review how to approach content creation and present some common pearls and pitfalls. <sup>RS</sup>

### REFERENCES

1. Smith A, Anderson M. Online shopping and e-commerce. Pew Research Center website. <https://www.pewinternet.org/2016/12/19/online-shopping-and-e-commerce/> Updated December 19, 2016. Accessed May 6, 2019.
2. Holliday AM, Kachalia A, Meyer GS, Sequist TD. Physician and patient views on public physician rating websites: A cross-sectional study. *J Gen Intern Med*. 2017;32:626-631.

### Traumatic macular hole (Continued from page 17)



**Figure 2. Postoperative autofluorescence and optical coherence tomography show successful macular hole closure with human amniotic membrane (HAM) graft in place (A) and early overfill of retina onto the HAM (B).**

over the optic nerve to avoid displacing the HAM graft, and endotamponade was instilled. Although Dr. Rizzo has demonstrated effective closure of recurrent macular holes plugged with HAM using 20% SF-6 gas, in this case 1,000-cS silicone oil was used as the endotamponade due to the patient's monocular and aphakic status.

Optical coherence tomography and autofluorescence one week postoperatively demonstrated successful hole closure with maintained orientation of the HAM graft (Figure 2) and no signs of excessive intraocular inflammation.

Dr. Rizzo has reported follow-up beyond one year and hypothesized that secreted growth factors may stimulate retinal repair. This technique shows promise as an alternative for surgical closure of large, traumatic and/or recurrent macular holes. <sup>RS</sup>

### REFERENCE

1. Rizzo S, Caporossi T, Tartaro R, et al. A human amniotic membrane plug to promote retinal breaks repair and recurrent macular hole closure. *Retina*. 2018;00:1-9.



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**Reference: 1.** Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. *Adv Drug Deliv Rev.* 2018;126:58-66.

MMM-0038 02/19

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