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Year of uncertainty

2020 has been filled with many things, uncertainty being the common denominator. Masks, respirators, lockdowns, home-learning, time to a COVID-19 vaccine and herd immunity, the economy, social injustice and the election, to name a few. Enveloped with uncertainty, we often think unrealistically about outcomes, projecting catastrophically. We overestimate the negative impact an event will have on our happiness. Fortunately, the science of “affective forecasting” assures us that we’re poor judges of our future emotions and the impact of specific events on them.

Uncertainties also run rampant through our retina clinics. Which proliferative diabetic retinopathy patient will be noncompliant and go needlessly blind? Which injection patient will develop endophthalmitis? Which patient on hydroxychloroquine will develop irreversible retinal toxicity? (See page 34.) Which retinal detachment patient will develop proliferative vitreoretinopathy and re-detach? Which large macular hole will need an advanced surgical technique for successful closure? (See page 18.)

The stress that so readily accompanies chronic uncertainty can slowly erode the quality of our lives. It’s easy to ignore these stresses. It’s human nature to think everybody else is stressed while I’m just fine, thank you.

We can’t change the magnitude of the external, unpredictable uncertainties that cascade into our lives, nor the rate at which they emerge onto our landscapes. But we can control our approach to dealing with them.

First, we can recognize the uncertainties and associated stresses as real. Acknowledge and validate rather than deny and ignore.

Second, we can carve out time daily for personally meaningful activities that we control. Go for a walk, connect with friends and family, meditate, exercise, show appreciation, disconnect from Facebook and social media.

Third, and maybe most difficult, consider mentally reframing the situation. Winston Churchill said, “Never let a good crisis go to waste,” at the founding of the United Nations in the aftermath of World War II. See page 41 where Dr. Andrew Schimel tells an incredible family tale from that era and gives concrete approaches to improving our quality of life today.

Yes it can be overwhelming. But someday we’ll look back on this and tell our kids and grandkids the story of this unique moment in history. We have the privilege of living through these challenging times, and inherent with that comes the responsibility to support ourselves and those around us as we overcome one uncertainty after another. 😊
# Features

## Cover Story: Human Amniotic Membrane as an Emerging Option for Macular Holes

Human amniotic membrane (hAM) shows promise as a superior scaffold for wound healing.

By Aliaa H. Abdelhakim, MD, PhD, and Tongalp H. Tezel, MD

## 10 Answers about PCV and Anti-VEGF Resistance

How to diagnose and manage polypoidal choroidal vasculopathy.

By Gregg To Kokame, MD, MMM, Jase N. Omizo and Kelli A. Kokame

## The Shifting Paradigm of HCQ Retinopathy

Cases of hydroxychloroquine toxicity can be progressive even after drug cessation.

By Summer Samuels and Raj K. Maturi, MD

## Protocol V Lessons on Observation for CI-DME

Exploring the management of center-involved diabetic macular edema with good vision.

By Mohamed Ashraf, MD, PhD, and Jennifer K. Sun, MD, MPH

## Essay: Coping in the COVID-19 Era

Guidance for dealing with stresses of the times

Do the right thing, focus on connections, reexamine your life and know that we’re going to be OK.

By Andrew Schimel, MD
A rocky year after approval, brolucizumab finds its niche

It was a year ago that Novartis received regulatory approval for Beovu (brolucizumab) for treatment of wet age-related macular degeneration and launched a robust marketing campaign at the American Academy of Ophthalmology meeting in San Francisco. After a rocky year, retina specialists have reconsidered brolucizumab not so much as a first-line therapy, but as a niche treatment for select patients.

At last year’s AAO Subspecialty Day, it seemed Beovu ads covered every escalator and Beovu banners hung from every ceiling at Moscone Center West. What happened three months later is well known in retina lore. The American Society of Retina Specialists issued an update alerting members to reports of retinal vasculitis (RV) linked to brolucizumab. In May Phillip J. Rosenfeld, MD, PhD, of Bascom Palmer Eye Institute, and David J. Browning, MD, of Charlotte Eye Ear Nose and Throat Associates, co-authored a scathing editorial—“Is this a 737 Max Moment for Brolucizumab?”—calling for a moratorium on its use.1

Novartis launched its own tri-level safety review: gathering clinical data from physicians reporting events; using its data monitoring committee, a standing group that evaluates post-marketing and clinical trial data; and launching an external safety review committee. At AAO 2020, Novartis reported the results of that review. The upshot is that patients with a history of intraocular inflammation or retinal vascular occlusion (RO) had an almost tenfold higher risk of RV/RO, 3.97 percent vs. 0.46 percent among all patients within six months of starting treatment.2

Finding its place

In the meantime, it seems brolucizumab may have found its place. At the Ophthalmology Innovation Summit virtual Retina Innovation Showcase, a panel of four high-profile retina specialists described how they’re continuing to use brolucizumab in their practices.3

Panel moderator John Pollack, MD, a partner at Illinois Retina Associates and assistant professor at Rush University Medical Center in Chicago, asked them two questions:
• Should professional organizations declare a moratorium on brolucizumab?
• In what subset of patients is brolucizumab a reasonable treatment option?

No to moratorium

To a person, they decried the idea of moratorium. Allen C. Ho, MD, director of retina research at Wills Eye Hospital, Philadelphia, credited Novartis for taking a “very
transient” approach to investigate the reports of retinal vasculitis attributed to brolucizumab.

“I don’t think any society should be a determinant of whether or not something remains approved,” Dr. Ho said. “This is a regulatory process. Let’s see how this plays out.”

As for the second question, here’s how the panelists answered.

An effective drying agent

Peter Kaiser, MD, professor, Cole Eye Institute, Cleveland:

“Sort of lost through all of this is that [brolucizumab] is an incredible drying agent, and it may not necessarily lead to better outcomes—as HAWK and HARRIER didn’t show that—but certainly it’s drying the retina very impressively in the patients in whom I’d considered using it.” That includes patients who had retinal fluid on monthly aflibercept (Eylea, Regeneron Pharmaceuticals).

“We are learning a lot more about this inflammation,” Dr. Kaiser added. “It seems to occur more in females over males. We don’t know why yet, and we’re looking at the idea that perhaps this has something to do with an anti-drug antibody, but more data are needed.” (Dr. Kaiser is a member of Novartis’ brolucizumab safety review committee.)

Refractory patient

Marco Zarbin, MD, PhD, professor and chair of ophthalmology, New Jersey Medical School, Newark: “This would not be my lead drug for a unilateral patient or for a patient who’s responding to the current therapy, or for a patient who’s never been treated before.”

But brolucizumab could be considered for a bilateral patient who’s not responding to therapy, he said, with other caveats: if the injection frequency isn’t a burden or if the patient is male.

“When I do use it, I monitor the patient more frequently after the injection because, although they’re very good at picking up the symptoms of floaters, for example, there could be things like cotton wool spots and small areas of vasculitis that are going to be asymptomatic but that I can see.” He added that “early very aggressive steroid therapy” may mitigate adverse events.

When all else fails

Christina Y. Weng, MD, MBA, associate professor, Baylor College of Medicine, Houston: “I still think that it holds a spot for a certain subset of patients.” She doesn’t use brolucizumab as an option in treatment-naïve patients. “But for patients who have failed all the other existing agents, is brolucizumab a better choice than having persistent fluid and vision loss in the alternative? I think it is.”

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Quotable

“But for patients who have failed all the other existing agents, is brolucizumab a better choice than having persistent fluid and vision loss in the alternative? I think it is.”

— Christina Y. Weng, MD, MBA

REFERENCES

Discover continuous calm in uveitis

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

- **Proven to reduce uveitis recurrence at 6 and 12 months**
  
  [At 6 months–18% for YUTIQ and 79% for sham for study 1 and 22% for YUTIQ and 54% for sham for study 2 (P<.01). At 12 months–28% for YUTIQ and 86% for sham for study 1 and 33% for YUTIQ and 60% for sham for study 2.]

- **Innovative Durasert® technology is designed for a sustained release of fluocinolone acetonide for up to 36 months with just 1 YUTIQ implant**

**INDICATIONS AND USAGE**

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

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

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

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

**WARNINGS AND PRECAUTIONS**

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

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

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

**ADVERSE REACTIONS**

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

**References:**

1. **YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018.**

**For more information, visit YUTIQ.com**
YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

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

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

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

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

<table>
<thead>
<tr>
<th>ADVERSE REACTIONS</th>
<th>YUTIQ (N=226 Eyes) n (%)</th>
<th>Sham Injection (N=94 Eyes) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catarrh1</td>
<td>63/113 (56%)</td>
<td>13/56 (23%)</td>
</tr>
<tr>
<td>Visual Acuity Reduced</td>
<td>33 (15%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Macular Edema</td>
<td>25 (11%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>22 (10%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Conjunctival Hemorrhage</td>
<td>17 (8%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye Pain</td>
<td>17 (8%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Hypotony Of Eye</td>
<td>16 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>12 (5%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Dry Eye</td>
<td>10 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Vitreous Opacities</td>
<td>9 (4%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>9 (4%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Posterior Capsule Opacification</td>
<td>8 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Ocular Hyperemia</td>
<td>8 (4%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Vitreous Haze</td>
<td>7 (3%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Foreign Body Sensation In Eyes</td>
<td>7 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Vitritis</td>
<td>6 (3%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Vitreous Floaters</td>
<td>6 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye Pruritus</td>
<td>6 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Conjunctival Hyperemia</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Ocular Discomfort</td>
<td>5 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Macular Fibrosis</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Photopsia</td>
<td>4 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

(continued)

Table 2: Summary of Elevated IOP Related Adverse Reactions

<table>
<thead>
<tr>
<th>ADVERSE REACTIONS</th>
<th>YUTIQ (N=226 Eyes) n (%)</th>
<th>Sham (N=94 Eyes) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP elevation ≥ 10 mmHg from Baseline</td>
<td>50 (22%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>IOP elevation &gt; 30 mmHg</td>
<td>28 (12%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Any IOP-lowering medication</td>
<td>98 (43%)</td>
<td>39 (41%)</td>
</tr>
<tr>
<td>Any surgical intervention for elevated IOP</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

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

Manufactured by: EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA Patented.
Giant retinal tear surgery made simple

Perfluoro-n-octane as a short-term tamponade for repair of a rhegmatogenous retinal detachment with a GRT.

Rhegmatogenous retinal detachment secondary to giant retinal tear is associated with a relatively high rate of retinal redetachment.\(^1\)\(^,\)\(^2\) The rate of recurrent retinal detachment secondary to proliferative vitreoretinopathy and/or slippage has been reported to be as high as 40 to 50 percent after the first surgery with small-gauge vitrectomy and long-term gas or silicone oil tamponade.\(^2\)\(^,\)\(^3\)

Proliferative vitreoretinopathy (PVR) has been proposed to be more common with GRTs due to the extent of retinal break, extensive retinal pigment epithelium exposure as well as the younger average age of affected patients. Slippage, which may be due to incomplete drainage of subretinal fluid, occurs when re-attached retina and GRT slip posteriorly, leading to retinal folds or redetachment.

Pioneering PFCL in RRD with GRT repair

Intraoperative use of perfluorocarbon liquid (PFCL), first described in 1987 by Stanley Chang, MD,\(^4\) has helped increase intraoperative reattachment in RRD with GRT in the presence or absence of PVR.\(^2\)\(^,\)\(^3\) Perfluoro-n-octane (PFO), the most commonly used PFCL today, has a very high specific gravity (1.76), viscosity and low surface tension, which makes it an ideal agent in flattening retinal folds and preventing slippage. Direct intraoperative PFO-silicone oil exchange is one option to mitigate slippage, as we have reviewed here previously (June 2017 Retina Specialist, page 41).

Ferdinando Bottoni, MD, and colleagues at the University of Milan first described the use of PFO as a postoperative tamponade in 1994.\(^5\) They demonstrated a single-surgery anatomical success (SSAS) rate of 82 percent until at least three months of follow-up.

Since then, many authors have retrospectively reported their outcomes with the postoperative use of PFO from an average of five to 18 days (Table, page 11).\(^5\)\(^,\)\(^13\) The SSAS rate with short- to medium-term postoperative PFO has been reported between 77.4 to 100 percent at three-month follow-up, notwithstanding the immediate second surgery to remove PFO.

Surgical technique

Preservative-free triamcinolone acetate (Triesence, Alcon) is used to visualize the vitreous to ensure a complete PVD and vitrectomy. In GRT, the vitreous base should

**View the Video**
be meticulously shaved anteriorly 360 degrees with scleral depression. The anterior part of the GRT flap can be trimmed to prevent anterior traction, PVR and possible peripheral ischemia. The video demonstrates these key steps in the technique.

Next, PFO is gradually injected as a single bubble over the optic disc, taking care to ensure the dual bore cannula remains within the bubble as it expands. We sometimes use chandelier endoillumination to allow for binannual PFO injection and unfolding of the GRT using a Tano diamond-dusted brush if the tear is scrolled at its anterior edge (Figure 1, page 9).

Next, we apply three confluent rows of laser to the posterior edges of the GRT. We like to also add scattered laser posterior to the most posterior row in a V pattern to treat the horns of the GRT extending to the ora serrata (Figure 2). Doing so prevents guttering of subretinal fluid and recurrent RRD. We often also add two rows of laser 360 degrees close to the ora serrata. Following this, the eye is topped off with a full fill of PFO (usually around 90 percent) until it reaches the trocars. Any residual vitreous fluid that remains behind the lens is exchanged for air in a minimal fluid-air exchange.

The eye is then flushed with SF6 gas (20%) to substitute air in the residual 5 to 10 percent volume of the vitreous not filled with PFO (Figure 3). We routinely close the sclerotomies with sutures to prevent any subconjunctival migration of PFO that would result in an underfill.

**Postoperative management**

We instruct the patient to lie supine 90 percent of the time postoperatively. Approximately seven to 10 days later, we take the patient back to the operating room to remove the PFO. Using a soft-tipped cannula, a fluid-air exchange is performed, with meticulous removal of any and all PFO bubbles in the posterior pole. If the patient is pseudophakic, an anterior or chamber washout may also be required to ensure no PFO bubbles remain in the anterior segment.

Next, we perform scleral depression to release any PFO bubble from the pars plana. This is a very important step as PFO bubbles may easily get trapped in the pars plana/plicata, much as emulsified silicone oil particles do. A fluid-air exchange is then completed with 100 percent air fill. The eye is then flushed with gas, either SF6 or C3F8.

**The PFO advantage**

Using PFO as a short-term tamponade for GRT has huge advantages. The most difficult step of GRT surgery is avoiding slippage, which occurs during removal of PFO in the fluid-air exchange.

Injecting PFO, laserimg under the PFO and closing the eye completely avoids this most difficult step of FAX since there’s no removal of PFO. Consequently, there’s no chance of slippage.

Moreover, laser can be applied to the GRT under very good visualization with PFO in situ. Surgical time is also minimized by removing the riskiest and time-consuming step of PFO removal, including the meticulous drying of the edge of the break to ensure no subretinal fluid or PFO remains at the end of the case.

---

**Five advantages of short-term perfluoro-n-octane for giant retinal tears**

- Avoids fluid-air exchange completely and, hence, avoids slippage.
- Laser is easier to perform under PFO than air.
- Minimal surgical time with no meticulous drying of subretinal fluid at the break or removal of PFO.
- Second surgery to remove PFO is straightforward.
- Postoperative positioning is easy for patients.
Even a direct PFO-silicone oil exchange still carries an opportunity for slippage because removal of PFO can result in some change in the position of the GRT and subsequent slippage. A short-term PFO tamponade avoids this risk completely and is our preferred technique.

Postoperative positioning is also quite easy for patients because they’re often more compliant positioning supine rather than staying face-down or on their side.

The second operation

For the second operation, around seven to 10 days after insertion of PFO, its removal is quite straightforward aside from needing to take time to find all the small bubbles that continue to emerge. We find using a high-magnification contact lens and a soft-tipped backflush cannula to passively remove these bubbles from the macular surface helps keep the process relatively straightforward.

In our experience, postoperative inflammation is minimal during the seven-day period with PFO in situ. We have,

### Studies of perfluoro-n-octane for rhegmatogenous retinal detachment secondary to giant retinal tear

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of study</th>
<th>Indication for perfluorocarbon liquid</th>
<th>Type of PFCL</th>
<th>Days</th>
<th>n</th>
<th>Single-surgery anatomical success</th>
<th>Tamponade</th>
<th>Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottoni, et al.²</td>
<td>1994</td>
<td>GRT</td>
<td>Perfluorodecalin</td>
<td>5</td>
<td>11</td>
<td>82%</td>
<td>air</td>
<td>NA</td>
</tr>
<tr>
<td>Rofail, et al.³</td>
<td>2005</td>
<td>GRT</td>
<td>Perfluoro-octane (PFO)</td>
<td>16.4</td>
<td>16</td>
<td>100%</td>
<td>C3F8</td>
<td>Cataract (6), epiretinal membrane (4), temporary hypotony (2), phthisis (1), inflammation (1)</td>
</tr>
<tr>
<td>Sirimaharaj, et al.²</td>
<td>2005</td>
<td>GRT</td>
<td>PFO</td>
<td>7.5</td>
<td>62</td>
<td>77.4%</td>
<td>SF6, C3F8 or silicone oil</td>
<td>Cataract, glaucoma (4.8)</td>
</tr>
<tr>
<td>Rush, et al.⁴</td>
<td>2012</td>
<td>GRT</td>
<td>PFO</td>
<td>11</td>
<td>10</td>
<td>90%</td>
<td>SF6, C3F8 or silicone oil</td>
<td>Posterior capsular opacifications (PCO), cataract, ERM</td>
</tr>
<tr>
<td>Randolph, et al.⁵</td>
<td>2015</td>
<td>GRT</td>
<td>PFO</td>
<td>18</td>
<td>23</td>
<td>78%</td>
<td>Air</td>
<td>Cataract (10), inflammation (7), transient intraocular pressure elevation (8)</td>
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<tr>
<td>Mikhail, et al.⁶</td>
<td>2017</td>
<td>GRT</td>
<td>PFO</td>
<td>6.7</td>
<td>30</td>
<td>86.4%</td>
<td>SF6, C2F6, C3F8, silicone oil</td>
<td>Anterior uveitis (6), glaucoma (1)</td>
</tr>
<tr>
<td>Eiger-Moscovich⁷</td>
<td>2017</td>
<td>GRT</td>
<td>PFO</td>
<td>10</td>
<td>13</td>
<td>92%</td>
<td>SF6, C3F8, silicone oil</td>
<td>Elevated IOP, cataract, cystoid macular edema</td>
</tr>
<tr>
<td>Zhang, et al.⁸</td>
<td>2018</td>
<td>GRT</td>
<td>Perfluorodecalin</td>
<td>8.4</td>
<td>23</td>
<td>100%</td>
<td>Air</td>
<td>cataract, PCO (69), inflammation, elevated IOP (5)</td>
</tr>
<tr>
<td>Sheridan, et al.⁹</td>
<td>2019</td>
<td>GRT</td>
<td>PFO</td>
<td>14.6</td>
<td>25</td>
<td>92%</td>
<td>SF6, BSS, air</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Days: days with postoperative PFO tamponade. N signifies the number of eyes. Tamponade is the postoperative tamponade agent after the second surgery.

Figure 3. The eye is flushed with SF6 gas (20%) to substitute air in the residual 5 to 10 percent volume of the vitreous not filled with perfluoro-octane.
however, noticed that phakic patients often have some worsening of cataract within the seven days, so it’s probably a good idea to consider cataract removal during the second surgery of PFO removal or soon afterward. All phakic patients in our series opted to undergo cataract extraction and intraocular lens implantation at the time of the second operation to remove the PFO.

Duration of postoperative PFO

In a literature review,^5^-^13^ postoperative PFO was removed on average at day 10.84. Most authors compared the advantage of longer-term tamponade with the possibility of PFO retinal toxicity in the form of outer plexiform changes, retinal compression, and cited complications such as elevated IOP and inflammation.

The rationale for keeping PFO for a minimum of six to seven days is that’s how long it takes to achieve the complete effect with laser retinopexy.

In our experience, an average of seven days with PFO was adequate to achieve long-term anatomical success. SSAS was 100 percent at three months’ follow-up in our series, a rate comparable to other small case-series of short-term postop PFO with RRD secondary to GRT with a similar follow-up length.^6^-^11^,^13^ Bottom line

PFO as a short-term postoperative tamponade agent in management of RRD secondary to GRT is safe and effective. The anatomical success rates with postop PFO (short to medium-term) are excellent. In our series the success rate was 100 percent, which is favorable compared to the reported success rates of 60 to 75 percent with gas or oil.

Phakic patients are candidates for early cataract surgery, perhaps at the time of PFO removal. Following PFO removal, long-term gas provides excellent tamponade and long-term anatomical success.

REFERENCES

A 71-year-old woman was referred to the University of Washington Medicine Eye Institute after receiving a new diagnosis of age-related macular degeneration by an outside provider. She denied any acute changes in her vision. Her ocular history only included upper-lid blepharoplasties. Her medical history was unremarkable and she wasn’t taking any systemic medications.

**Ocular examination findings**

On presentation, best-corrected Snellen visual acuity was 20/20 OD and 20/30 OS. Her pupils were equal and reactive without relative afferent pupillary defect, and her intraocular pressure was within normal limits in each eye. Confrontational visual fields and extraocular movements were full in both eyes. Her slit lamp exam was notable only for bilateral mild nuclear sclerosis.

The dilated fundus examination revealed macular pigmentary changes and drusen in both eyes. The far periphery of the left eye had several blot hemorrhages at 4 o’clock.

**Findings on imaging**

To further evaluate the focal peripheral retinal hemorrhages, we obtained color fundus photographs (Figure 1) and wide-field fluorescein angiography images.

FA of the left eye (Figure 2) demonstrated leakage on transit within the macula, consistent with a choroidal neovascular membrane from neovascular AMD. Optical coherence tomography imaging of the macula also demonstrated the CNVM with subretinal fluid associated with drusen.

The FA also showed patchy blockage of fluorescence between 4 and 5 o’clock corresponding to the retinal hemorrhages, sectoral peripheral capillary dropout, late peripheral leakage, and a venous tributary with delayed return, all in the inferotemporal quadrant.

**Diagnosis and management**

We diagnosed exudative macular degeneration based on the leakage pattern on FA and OCT. The patient responded well to serial intravitreal anti-VEGF injections.

Additionally, given the pattern of intraretinal hemorrhages and delayed return in an isolated venous tributary, we diagnosed an incidental retinal vein tributary, or “twig,” occlusion. Interestingly, the junction of the venous occlusion seemed to include not one but two arteriovenous (AV) crossings given its location at the branch...
We also obtained OCT through the AV crossings (Figure 3).

Because of the peripheral location of the twig retinal vein occlusion and the lack of other accompanying symptoms, we recommended observation. We also counseled the patient to follow up with her primary-care provider to optimize her cardiovascular health. She continued to follow up at our institution for the care of her AMD with no further complications attributable to her vein occlusion.

Etiology of ‘twigs’

RVO is one of the most common types of retinal vascular disease. It can be classified by the extent of the occlusion, with central vein occlusion being the most severe, followed by hemiretinal vein occlusion and branch RVO, which can further be subdivided based on involvement of first- or second-order vein tributaries. The latter includes central (macular) tributaries or, in the case of our patient, peripheral “twig” occlusions. These peripheral occlusions disrupt the least amount of retinal surface area and are accordingly less symptomatic.

Like other types of vein occlusions, the mechanism of a twig occlusion is thought to be disruption of normal endothelium and laminar blood flow. Most pathology occurs at AV crossings, where thick, rigid-walled arteries compress the more flexible thin-walled vein neighbors. This compression or obstruction, or both, leads to disruption in normal laminar blood flow, leading to thrombus formation.

Pathological processes such as arteriosclerosis that increase the thickness and rigidity of arterial walls are thought to be risk factors. Hypereosinophilic conditions also increase the risk of thrombosis formation and should be pursued in certain clinical presentations, where more typical risk factors are lacking.

In this patient with double AV crossings, development of a “twig” RVO provides circumstantial support for the presumed mechanism of injury. Given its stability and lack of other symptoms, we didn’t pursue further workup. A confounding point is that the patient continued treatment for her nAMD, and a lack of complications from the vein occlusion could be attributed to her ongoing anti-VEGF injections.

REFERENCES

Primary scleral buckle surgery is an important skill for any vitreoretinal surgeon. The use of chandelier illumination during scleral buckle surgery coupled with a microscope-based wide-angle viewing system (“chandelier buckle”) is increasing in popularity. For those interested in exploring this technique or refining their skills, we present six considerations for successful chandelier buckling (Figure).

• **Careful preoperative examination.** The chandelier should be placed 90 to 180 degrees from the area requiring best visualization (i.e., the site of the retinal breaks that need cryotherapy or the intended location of subretinal fluid drainage). Carefully examine the retinal detachment preoperatively to determine the best location for chandelier placement.

• **Trocar placement and management.** Insert the chandelier after isolating the rectus muscles and prior to cryotherapy. If possible, use a valved cannula to minimize the risk of vitreous prolapse. Place the trocar with a straight or minimally beveled insertion, which directs illumination toward the center of the vitreous cavity. Or, if you prefer a beveled approach, direct the chandelier toward the area of pathology.

During manipulation of the globe, ensure that the cannula doesn’t become dislodged by the silk sutures or the lid speculum. When removing the chandelier or its cannula, diligently check for and amputate any vitreous wicks. Have a low threshold to suture the sclerotomy. Some surgeons prefer to remove the cannula prior to tightening the buckle to minimize the risk of vitreous prolapse when the intraocular pressure is elevated. Consider applying a few spots of cryotherapy to the area immediately posterior or adjacent to the chandelier site with concern for undue vitreous traction.

• **Getting a peripheral view.** As with

**View the Video**

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**Bios**
Dr. Ali is a clinical associate with the Retina Group of Washington in Reston and Sterling, Va.

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

**DISCLOSURES:** Drs. Ali and Hahn have no relevant financial disclosures.
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Human amniotic membrane for macular hole surgery

This platform shows promise as a superior scaffold that enhances wound healing.

By Aliaa H. Abdelhakim, MD, PhD, and Tongalp H. Tezel, MD

Take-home points

» Macular holes are effectively problems of retinal wound healing, and large, chronic or refractory holes require a biologic scaffold to allow for guided migration of glial cells for controlled reapposition of the hole edges and subsequent closure.

» Human amniotic membrane (hAM) is derived from the innermost layer of the placenta and has demonstrated excellent utility for wound healing and closure in multiple anatomic locations in the eye, including macular holes.

» An in vitro model of human macular holes has shown higher glial activation marker expression as well as lower inflammatory marker expression when hAM is used as a scaffold for retinal hole closure compared to autologous retinal tissue grafts.

» Epimacular placement of hAM is sufficient to close macular holes and obviates the surgical trauma that would otherwise occur when stuffing the hAM directly into the macular hole.

Closure of a macular hole is accomplished by a coordinated wound healing response executed by activated neighboring glial cells. Proliferation and migration of activated glia are followed by their contraction, which leads to macular hole closure by reapposition of the edges of the retinal defect.1,3

It is well documented that small macular holes have the capacity of self-closure without surgical intervention, and that small macular holes that don’t heal spontaneously do well with the standard surgical approach of vitrectomy, internal limiting membrane peeling and gas endotamponade. These interventions augment the gliotic response needed for macular hole closure.4,6

For small macular holes, glial migration and macular hole closure occur relatively easily, as the defect is generally small and relatively acute. On average, the success rate of macular hole closure with surgery is around 90 percent.7 However, this closure rate has an inverse relationship with the size, chronicity and refractory status of the macular hole being operated on. Large, chronic or recurrent holes generally demonstrate lower closure rates.7, 8

Role of guided wound healing

In these more difficult cases, guided wound healing is generally the preferred approach. Surgical closure approaches to

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DISCLOSURES: Drs. Abdelhakim and Tezel have no relevant financial relationships to disclose.

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large or chronic holes entail the use of biologic scaffolds that allow for glial cell migration to traverse the large retinal defect in a controlled manner.

Here we report on the early experience with epiretinal human amniotic membrane (hAM) grafting in chronic, refractory macular holes. Human amniotic membrane appears to possess the ideal properties to correct the aberrant wound healing of a macular hole. It provides an anti-inflammatory, neurotrophic environment with a structural biologic scaffold for glial cell migration to facilitate wound closure.

**Alternative to biological scaffolds**

Several biologic scaffolds have received attention in recently described surgical methods to address large, myopic or chronic macular holes, including the inverted ILM flap, autologous ILM transplantation, anterior lens capsule flaps as well as the use of neurosensory retinal autologous transplantation of a neurosensory retinal flap for refractory holes.

An alternative is the use of hAM, which has proven successful as a scaffold for healing the cornea and conjunctiva. Only 20 to 50 µm thick and derived from the innermost layer of the placenta, hAM appears to be an ideal scaffold for wound healing, particularly within macular holes.

Not only does hAM provide a scaffold for controlled and guided gliosis, but it lacks immunogenicity, has anti-inflammatory and anti-angiogenic properties, is inert, and has been shown to support retinal pigment epithelium growth *in vitro*. Because of its anti-inflammatory and pro-healing tendencies, human amniotic membrane may in fact provide a biologic structural scaffold superior to even autologous tissues such as neurosensory retinal flaps.

**Higher levels of protein expression**

We conducted a study to compare the glial activation and inflammatory response induced by covering macular holes with autologous human retina explants or hAM.

We used 19 freshly harvested human cadaveric eyes, into which 1-mm circular holes were made.

These holes were then covered in an epiretinal fashion with 3-mm grafts consisting of hAM or autologous neurosensory retina (ANR), or were left uncovered for three days. We compared the gliotic reaction these graft states induced using a variety of methods aimed at detecting glial cell markers, including bone morphogenetic protein 7 (BMP7), glial fibrillary acidic protein (GFAP) and vimentin, within the explanted retina.

Western-blot techniques revealed that hAM expressed higher levels of BMP7, GFAP and vimentin compared to ANR, suggesting that the gliotic signaling response and recruitment with hAM is comparatively more robust at the translational level. One other marker we tested was...
expression of the SERPINA3 gene, which encodes for a serine protease inhibitor expressed during inflammation and as an acute phase protein. Using protein quantitation and immunohistochemical techniques, we found that this gene was more highly expressed in retinal holes covered with ANR compared to hAM, suggesting that hAM exhibited anti-inflammatory and likely pro-wound healing properties that bypassed the need for endogenous expression of acute phase proteins within the retina (Figure 1, page 19).

Taken together, these experiments show that hAM is in fact a more ideal biologic scaffold that provides the underlying retina with neurotrophic and anti-inflammatory signals that promote hole closure more robustly than autologous tissues.

**Emerging evidence for hAM**

Stanislao Rizzo, MD, and colleagues at the University of Florence recently popularized the use of hAM. They demonstrated the surgical technique of employing transplantation of human amniotic membrane into the subretinal space underneath recurrent macular holes with gas endotamponade resulted in good anatomic and visual outcome.

Other reports have used a similar technique of placement of hAM directly into the hole, with reports of postoperative parafoveal atrophy in 40 percent of patients. However, other groups have shown that placement of the amniotic membrane in an epimacular fashion under gas can also result in good outcome, with reattachment of retina as well as hole closure and improvement in visual acuity.

From a mechanistic perspective, an epimacular placement should work just as effectively with hAM, because all that’s needed is a scaffold to allow for guided glial cell migration. This type of placement is furthermore less traumatic to the macula because it bypasses the necessary trauma to the edges of the hole when stuffing the hAM into the defect.

In fact, using immunohistochemistry and our in vitro system described previously, we were able to demonstrate successful glial migration and subsequent reaposition of retinal wound edges through epiretinal coverage using hAM scaffold (Figure 2). This suggests that all that glial cells need to close the hole is a scaffold to guide migration over the hole rather than direct contact of the hAM with the walls of the hole.

Moreover, we devised a technique to address these macular hole-associated retinal detachments with staphyloma. This involves affixing a large amniotic membrane graft over the area of the macular hole and applying 5,000 centistoke silicone oil for endotamponade (Figure 3 and video).

Alternatively, stabilizing the hAM graft using a tissue glue made with the patient’s own plasma can prevent its dislodging should a gas tamponade be preferred at the end of the surgery. In our experience, this technique has resulted in excellent postoperative outcomes.

Human amniotic membrane appears to display the ideal properties to correct the aberrant wound healing of a macular hole. It provides an anti-inflammatory, neurotrophic environment, while also providing a structural biologic scaffold for glial cell
migration to facilitate wound closure.

**Bottom line**

Higher expression of glial cell activation markers, as well as decreased expression of anti-inflammatory markers in wounded retina covered with hAM suggests that for chronic, large and refractory holes, hAM may provide the best option for the desired surgical outcome.

We also recommend the use of hAM in an epimacular fashion rather than subretinal placement, given that glial cells can migrate across the hAM scaffold in an epimacular fashion and achieve hole closure effectively by bringing the hole edges together. This reduces surgical trauma to the photoreceptors in the macula, preserving the best possible visual acuity.

**REFERENCES**


Despite the marked improvement anti-VEGF injections have meant in the prognosis of patients with exudative macular degeneration, many patients continue to have persistent disease activity regardless of frequent injections. This raises a number of questions about predicting the effectiveness of anti-VEGF medications. Wouldn’t a marker that predicted anti-VEGF resistance be helpful in planning and following the care of patients with exudative macular degeneration? What if an alternative treatment existed that actually resulted in better vision than anti-VEGF monotherapy at two years? Wouldn’t that be a huge help in determining which drug to start with in the management of exudative macular degeneration?

Pathophysiology of PCV

That marker may be polypoidal choroidal vasculopathy, also known as subretinal neovascularization with aneurysmal dilations. This subtype of exudative macular degeneration usually manifests as type I choroidal neovascularization between Bruch’s membrane and the retinal pigment epithelium. However, it can also have type II characteristics in which the CNV breaks through the RPE into the subretinal space.

What if this marker also showed that response was better with one specific anti-VEGF drug? Wouldn’t that be a huge help in determining which drug to start with in the management of exudative macular degeneration?
be a type I subretinal NV under the RPE and above Bruch’s membrane. Type II subretinal NV occurs above the RPE and in the subretinal space. Type III NV, or retinal angiomatous proliferation (RAP), includes an intraretinal component.

The clinical presenting features of this aneurysmal form of CNV look very similar to what we see with exudative age-related macular degeneration: subretinal fluid and blood, as well as associated subretinal exudate and retinal pigment epithelial detachment (RPED).

PCV has some distinguishing clinical features compared to exudative AMD:
- more subretinal fluid;
- higher height of subretinal fluid;
- more RPED;
- less intraretinal fluid or macular edema; and
- higher frequency of subretinal hemorrhage.

However, unlike with typical exudative AMD, the PCV diagnosis can’t be purely based on fundus examination or fluorescein angiography. FA in PCV for most cases shows occult leakage or occult CNV often associated with RPED (Figure 1 B, C).

Isn’t PCV mainly a disease among Asians?

PCV has been diagnosed with high prevalence in Asian populations. However, PCV in Caucasians has been underdiagnosed due to a lack of access to, or interest in, indocyanine green angiography. Initial studies reported the prevalence of PCV in Caucasians to be less than 10 percent, but these studies were done with digital fundus camera ICGA, which is much less sensitive than the scanning laser ophthalmoscope (SLO) ICGA. SLO ICGA in Caucasian groups showed the prevalence of PCV ranged from 20 percent in a Duke study to 24.5 percent in a study of a patient population with predominantly European ancestry from Brazil, and as high as 31 percent in a Caucasian population in Hawaii.

ICGA is the best way to diagnose PCV due to its ability to delineate the aneurysmal lesions in the CNV complex with the highest sensitivity. The aneurysmal lesions are best seen three to five minutes after ICG dye injection. A hypofluorescent ring often surrounds them.

Video ICGA with the SLO may show the infrequent but dramatic finding of pulsations of the polypoidal lesions diagnostic of PCV. RPED is a frequent finding associated with PCV (Figure 1 A, D–F). The RPED may mask the aneurysmal lesions, especially with the usual hypofluorescence noted in the area of the RPED on SLO ICGA (Figure 1 E, F). PCV lesions often appear at the edge of or at a notch in the RPED.

A frequent finding is a branching vascular network (BVN) connected to the polypoidal lesions. SLO ICGA is the most sensitive imaging modality for visualizing polypoidal lesions and the BVN, which makes it more suitable for diagnosing PCV than flash fundus camera ICGA.
**Polypoidal choroidal vasculopathy**

**Why is PCV important to diagnose? Doesn’t it respond the same way as exudative AMD to our standard-of-care treatments?**

No genetic markers now exist for anti-VEGF resistance. However, one phenotypic marker is predictive of anti-VEGF resistance: subretinal aneurysmal lesions in the CNV complex, or PCV. While case studies first identified this, subsequent studies have confirmed a significantly higher rate of persistent disease activity in eyes with PCV when treated with the currently available anti-VEGF agents.

This was seen in a study of pro re nata ranibizumab (Lucentis, Genentech/Roche) treatment in Switzerland as well as a retrospective U.S. study that defined anti-VEGF resistance as lack of clinical response after four consecutive injections and showed a statistically significant higher prevalence of anti-VEGF resistance associated with PCV in both Asian and Caucasian patients. In fact, PCV was an even stronger predictor of anti-VEGF resistance in Caucasian vs. Asian patients. Thus, polypoidal or subretinal aneurysmal lesions associated with subretinal neovascularization is the one phenotypic marker predictive of anti-VEGF resistance.

**Is there another treatment option for eyes resistant to anti-VEGF agents?***

Because PCV may not respond to anti-VEGF medications, alternative treatments may need to be considered, especially if a patient exhibits a poor response to therapy. Recently published two-year results of the EVEREST II trial showed that primary treatment of combination photodynamic therapy (PDT) with anti-VEGF injection was superior to anti-VEGF monotherapy alone both in terms of anatomic response with closure of polypoidal lesions and visual improvement. In addition, at two years treatment burden was half of that of anti-VEGF monotherapy (12 vs. six injections).

In addition to primary combination therapy of PDT and anti-VEGF therapy, eyes treated initially with anti-VEGF but with a poor response may have a better outcome with less treatment burden when subsequently treated with combination PDT. (See case examples on pages 29 and 30.)

**How do we best diagnose the polypoidal or aneurysmal lesions within subretinal NV?***

ICGA has been the gold standard for diagnosing polypoidal subretinal aneurysmal lesions in the subretinal neovascular complex, and SLO ICGA has greater sensitivity than digital fundus camera ICGA. However, if ICGA isn’t available, the diagnosis can be made using an imaging modality that has high specificity but lower sensitivity than ICGA. OCTA images the BVN well, although aneurysmal or

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**Figure 2.** Optical coherence tomography angiography (A) shows the branching vascular network; the polypoidal or aneurysmal dilations are less evident. B-scan OCT (B) shows the corresponding location of OCTA images as the area between the retinal pigment epithelium and Bruch’s membrane (purple tracing lines). Note the prominent subretinal fluid and lack of intraretinal cystic changes more common in polypoidal choroidal vasculopathy. Indocyanine green angiography (C) shows a vascular complex with hyperfluorescent dilations. Multimodal imaging with corresponding B-scan (D) shows the typical inverted U-shaped elevation with heterogeneous reflectivity consistent with a polypoidal lesion.
polypoidal lesions are less discerning due to slower blood flow within the polypoidal lesions (Figure 2).21-22

En face OCT can often demonstrate the BVN and the aneurysmal dilations associated with PCV anatomically (Figure 3).21,23-24 But, again, it’s less sensitive than ICGA. B-scan OCT is the most available diagnostic modality in most practices, and shows fluid and blood associated with the polypoidal lesions.21-22 The polypoidal lesions most diagnostic of PCV appear as inverted U-shaped lesions with heterogeneous reflectivity, while the BVN appears as a shallow elevation of the RPE above Bruch’s membrane (double-line sign).4

Practically, we recommend using any diagnostic means available to identify subretinal aneurysmal lesions, especially if the patient responds poorly to anti-VEGF therapy. Start with OCT B-scan, and don’t look just at the change images or the OCT map. Look for a double-line sign at the individual horizontal and vertical scans for areas suspicious for the BVN often with overlying fluid (Figure 4). Then look for polypoidal lesions and an inverted U-shaped elevation with heterogeneous reflectivity with B-scan OCT going through the lesions (Figures 2 to 4). These findings can resolve after anti-VEGF therapy, so it’s important to look at the B-scan OCT images before beginning anti-VEGF therapy.

The best way to fully evaluate an area with OCT is to perform the sequential raster scan, which allows you to scroll down through the entire macular with B-scan OCT. The en face mode is available on most OCT platforms and can be utilized from preexisting OCT data to scan a layer between the RPE and Bruch’s membrane, or between the outer retina and the choriocapillaris (ORCC). This may allow imaging of the BVN with the diagnostic polypoidal lesions or aneurysmal dilations.

OCTA localized to the area between the RPE and Bruch’s membrane or the ORCC cut may provide diagnostic pictures (Figure 2), but the polypoidal lesions tend to have low flow and may not visualize well with OCTA.19 However, multimodal imaging may identify the polypoidal lesions on B-scan when combined with en face OCT or OCTA (Figure 2).

5 How does PCV treatment differ from that for wet AMD?

Based on the EVEREST II study, a reasonable approach is anti-VEGF therapy combined with PDT for PCV that involves the central fovea.17-19 Practically, if vision is still very good (20/40 to 20/50 or better),
Confidence in Demonstrated Safety Data Across 4 FDA-Approved Indications

WET AMD, DME, DR, and MEfRVO

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anti-VEGF = anti-vascular endothelial growth factor; AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; DR = Diabetic Retinopathy; MEfRVO = Macular Edema following Retinal Vein Occlusion.

IMPORTANT SAFETY INFORMATION AND INDICATIONS

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

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


Please see Brief Summary of Prescribing Information on the following page.
WARNINGS AND PRECAUTIONS (cont’d)

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

ADVERSE REACTIONS

• Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

• The most common adverse reactions (>5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

INDICATIONS

EYLEA® (afiblercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).
BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.us for additional information.

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).

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
4.2 Active Intravitreal Inflammation
4.3 Hypersensitivity
4.4 Intraocular Inflammation
4.5 Endophthalmitis and Retinal Detachments

6.2 Intraocular Pressure

6.5 Thoracoabdominal Events

6.6 Clinical Trials Experience

8 USE IN SPECIFIC POPULATIONS
8.3 Pediatric Use

8.4 Geriatric Use

8.5 Pregnancy

8.6 Lactation

8.7 Nursing Mothers

8.8 Carcinogenesis, Mutagenesis, Impairment of Fertility

8.9 Pregnancy

8.10 Embryonic-Lethal, Teratogenic, and Carcinogenic Potential

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Polypoidal choroidal vasculopathy

anti-VEGF therapy is a reasonable approach to start. However, if vision is 20/50 to 20/60 or worse, combination PDT and anti-VEGF therapy initially is a reasonable approach. In EVEREST II, combination PDT/anti-VEGF showed better results for treatment burden and visual recovery.

EVEREST II had no cases of sudden vision loss after full-fluence PDT. The trial did report a potential risk of choroidal ischemia or subretinal hemorrhage after PDT treatment, but this risk is small and is probably less than it is in typical exudative AMD due to the associated thick choroid. Especially if lesions are extrafoveal and the PDT lesion spot can avoid the fovea, combination PDT/anti-VEGF with the laser spot size sparing the fovea is a reasonable approach.

Does PCV respond as well to anti-VEGF as typical exudative AMD?

The response of typical exudative AMD to anti-VEGF therapy has been significantly better than the natural course of the disease, resulting in markedly less subretinal hemorrhage and leakage as well as better overall vision outcomes. However, case series and retrospective studies have shown the PCV subtype has a higher risk of anti-VEGF resistance.13-16 PCV eyes

Case: Primary combination PDT

An 85-year-old man presented with blurred vision in the right eye for five months. Visual acuity was 20/60. He had a retinal pigment epithelial detachment (RPED), serous retinal detachment, pachydrusen and subretinal exudates (Figure 1, page 23).

Indocyanine green angiography revealed a branching vascular network (BVN) and polypoidal aneurysmal lesions in the superotemporal macula. The patient refused frequent intravitreal anti-VEGF therapy. He specifically requested a therapy to minimize treatment burden and injections. He had full-fluence photodynamic therapy with intravitreal bevacizumab 1.25 mg and dexamethasone 400 µg.

The lesion responded dramatically. Slight residual RPED and subretinal fluid remained, but after two subsequent bevacizumab and dexamethasone injections, the RPED resolved, as did the subretinal fluid and exude (Figure 5). Vision recovered to 20/30 and he has not needed further injections or PDT in six years (Figure 6).

Figure 5. After combination photodynamic therapy, infrared photography (A) shows a raster scan with the blue arrow showing the location of the B-scan optical coherence tomography through the fovea (B), which shows marked resolution of intraretinal edema, retinal pigment epithelium detachment and subretinal fluid.

Figure 6. Indocyanine green angiography (A) six years after combination photodynamic therapy shows a superotemporal retinal pigment epithelium scar with the corresponding optical coherence tomography through the fovea. The corresponding OCT (B) goes through the RPE scar area and the previous polypoidal choroidal vasculopathy. Note the area of RPE atrophy corresponding to the scar (arrowheads) and the double-line sign corresponding to the residual branching vascular network (BVN) (arrow). Early (C) and late-phase (D) fluorescein angiography shows no leakage. ICGA (E) shows regression of the PCV complex but residual BVN.
A 96-year-old man was diagnosed with exudative age-related macular degeneration with a vascularized retinal pigment epithelial detachment (RPED), subretinal fluid, macular cystic changes, and subretinal hyper-reflective material. Fluorescein angiography showed occult leakage. Despite monthly aflibercept (Eylea, Regeneron Pharmaceuticals), the patient had persistent subretinal fluid, subretinal hemorrhage, RPED and subretinal exudates. Indocyanine green angiography aided in diagnosing the polypoidal subtype of exudative AMD. ICGA helped to guide photodynamic therapy and measure the spot size (Figure 7).

Vision was 20/40 and the lesion was subfoveal so reduced-fluence PDT was performed, but the leakage persisted and vision decreased to 20/60. Three months after the first PDT treatment, the patient had full-fluence PDT combined with same-day bevacizumab 1.25 mg (Avastin, Genentech/Roche) and dexamethasone 400 µg. The RPED, macular edema and subretinal fluid showed marked resolution, and the patient now requires aflibercept injections every three months (Figure 8). Vision has recovered to 20/40.

Is combination PDT/anti-VEGF for PCV different from that for typical exudative AMD?

In the early 2000s, FA was used to determine lesion size in typical wet AMD and the area of leakage was delineated. The greatest linear dimension was calculated based on leakage on FA. The initial recommendation was to use a treatment spot 1,000 µm larger than the greatest linear dimension leakage on the FA for typical exudative AMD. This involved a large area, including significant adjacent normal RPE. PDT treatment for PCV lesions as performed in the EVEREST II study is very different. The PCV spot size for PDT is based on ICGA, not FA. The area of BVN and the polypoidal lesions is encircled. The greatest linear dimension is then determined on ICGA. Some experts use a treatment spot size exactly the size of the PCV lesion on ICGA. However, it’s also reasonable to add a 300-µm border around the lesion on ICGA.

For verteporfin (Visudyne, Bausch +...
Lomb), an intravenous dose of 6 mg/m² is given and the diode laser (689 nm) is directed to the treatment area 15 minutes after intravenous dye infusion. If the PCV lesion is extrafoveal, we recommend full-fluence PDT (50 J/cm² at 600 mW/cm² for 83 seconds). If the lesion is subfoveal and vision is good, then reduced-fluence PDT (25 J/cm² at 300 mW/cm²) can be considered.

Laser-spot duration is 83 seconds for both full-fluence and reduced-fluence treatment, but the laser settings are different as noted previously. If vision is 20/50 to 20/60 or worse, full-fluence treatment is reasonable for subfoveal lesions based on the EVEREST II study.

**Does macular laser photo-coagulation of polypoidal lesions have a role in PCV therapy?**

If the diagnosis of PCV is made with extrafoveal polypoidal lesions resulting in leakage, focal macular laser treatment to the polypoidal lesions is reasonable with or without supplemental anti-VEGF therapy. This may stabilize the leakage long-term with good vision. The goal of thermal laser is to close the polypoidal lesion and prevent further leakage or bleeding.

**Among ethnic populations, do the presenting characteristics of PCV differ?**

PCV was initially described as a peripapillary disease in Caucasian and Black patients and often bilateral. More recent studies in Caucasians showed that PCV primarily affects the macula. In Caucasians with unilateral disease, significant drusen and geographic atrophy can present in the fellow eye (Figure 9A), and peripapillary disease provides a characteristic peripapillary scarring around the nerve (Figure 9B), which doesn’t usually occur in Asian patients with this disease.

Although typical exudative AMD has long been known to be more frequent in females, PCV has a strong male predilection in Asians vs. the usual female predominance of typical exudative AMD in Caucasians. PCV in Blacks often has larger caliber vessels and is more often peripapillary.

**So what role does diagnosing PCV in exudative AMD patients have in my practice?**

Although most patients with exudative AMD receive anti-VEGF as first-line therapy, PCV is the one subtype of exudative AMD that may predict anti-VEGF resistance.

If a patient with exudative AMD has a poor response to first-line anti-VEGF therapy, alternative treatment with combination PDT/anti-VEGF injection can be considered. However, if only B-scan OCT is available, polypoidal or aneurysmal lesions may regress after long-term anti-VEGF therapy, making the diagnosis of PCV more difficult.

In addition, EVEREST II has shown that combination therapy with PDT should be considered as a primary treatment for PCV because it yields better vision and anatomical results than ranibizumab alone. Finally, PCV may be more responsive to certain anti-VEGF medications. Aflibercept (Eylea, Regeneron Pharmaceuticals) is the treatment of choice in Asia for PCV; it has shown a significantly better response in some eyes treated.
previously with other anti-VEGF agents and, in the PEARL II trial, even in patients previously treated with high-dose ranibizumab.

In the future, there could also be treatment response differences with newer medications, such as broocizumab (Beovu, Novartis), based on treatment responses in the HAWK and HARRIER trials, as well as anticipated results from the ongoing Merlin trial for previously treated anti-VEGF-resistant exudative AMD.

**Bottom line**

PCV is the most impactful subtype of exudative AMD because it provides a marker for anti-VEGF-resistance, which may affect therapeutic planning for treatment-naïve eyes as well as eyes responding poorly to anti-VEGF therapy. Combination PDT/anti-VEGF therapy can significantly decrease treatment burden and improve anatomic and visual outcomes. Although SLO ICGA is the gold standard for diagnosing PCV, retina specialists should use all modalities, including B-scan OCT, en face OCT and OCTA, to make the diagnosis. While common in Asian patients, PCV is more common in Caucasian patients than previously thought (20 to 30 percent of exudative AMD).

**REFERENCES**


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**Tips on chandelier buckling (Continued from page 16)**

Surgical Pearls: Tips on Chandelier Buckling

- **Tip 1**: When using a chandelier buckling technique, consider the orientation of the scleral buckle as well as the position of the eye. Ensure that the chandelier is properly aligned with the incision site to allow for accurate placement of the buckle.s

- **Tip 2**: Use a combination of chandelier buckling techniques to achieve the desired anatomical result. This may involve the use of a single-gauge needle, a No. 11 blade, or a combination of these devices.

- **Tip 3**: To ensure proper clarity and symmetry, carefully suture the scleral suture in place before releasing the chandelier. This helps to prevent any potential displacement or misalignment of the buckle.

- **Tip 4**: Remember that the goal of chandelier buckling is to achieve the desired anatomical result while minimizing any potential complications. This may require the use of a combination of chandelier buckling techniques to achieve the desired results.

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**PEARL VIDEO**

A video demonstrating the use of a chandelier buckling technique is available. To access the video, visit the following link: [Chandelier Buckling Video](#).
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While hydroxychloroquine retinopathy is generally considered rare, a large study found that the overall prevalence of HCQ retinopathy was 7.5 percent in patients who used HCQ continuously for more than five years, increasing to around 20 percent after 20 years of therapy.¹

We describe the main risk factors for HCQ retinopathy, detail the progression of the condition even after drug cessation and summarize the proposed mechanisms of toxicity in this condition.

Reducing risk of HCQ retinopathy

To reduce the prevalence of HCQ, or Plaquenil, retinopathy, the current guidelines for HCQ prescriptions recommend ≤5 mg/kg real body weight. In usage, this translates to a minimum patient weight of 176 pounds to tolerate the typical daily dose of 400 mg. During the first five years of treatment at this recommended level, the risk for HCQ retinopathy development is less than 1 percent.² At up to 10 years, the rate is less than 2 percent, but it rises to almost 20 percent after 20 years.²

Thus, this more conservative treatment protocol reduces the HCQ toxicity risk early (in the first 10 years), but it doesn’t reduce the risk if the patient has been on therapy for 20 years or more.

Screening for HCQ retinopathy should include multifocal electroretinography and fundus autofluorescence when therapy starts, then yearly after five years of treatment, along with annual spectral-domain optical coherence tomography and 10-2 visual fields after therapy starts (Table).

Here, we report on a case of Plaquenil retinopathy and review the literature.

Case: Progression after halting HCQ

We examined a 56-year-old patient
who had used Plaquenil for 13 years and who was noted to have retinopathy. She described having a “sparkly C-shaped” image in her right eye for the previous two years before her first examination. Despite immediate discontinuation of HCQ, she has continued to have progressively worse night vision and subjective contrast sensitivity over three years of follow-up. The progression is most easily noted in worsening retinal pigment epithelium autofluorescence (Figure 1). Spectral-domain optical coherence tomography performed at baseline confirmed generalized retinal thinning with loss of the foveal inner/outer segment junction (Figure 2, page 36). Almost all nine subfields of the macular thickness map for both eyes showed thinning (Figure 3A, page 37). Multifocal ERG confirmed significant loss of foveal function with decreased central waveforms in each eye (Figure 3B).

Qualitative visual changes

We’ve found common symptoms among our HCQ retinopathy patients to be generally limited to the central visual field. They include:

- flashing lights in the center;
- central blurriness;
- central loss of contrast; and
- difficulty reading despite having excellent Snellen acuity.

Mihai Mititelu, MD, MPH, and colleagues studied qualitative vision changes in their HCQ patients.5 Five of their seven patients had complaints relating to night vision and blind spots, and declining visual acuity. Most of the symptoms developed after anatomic changes had occurred.

HCQ mechanisms of action

Hydroxychloroquine is an antimalarial drug often used to help treat rheumatoid arthritis, systemic lupus erythematosus and other autoimmune diseases. It has...
HCQ binds strongly to melanin in the RPE and uvea, and is therefore highly concentrated in these tissues—up to 10,000 times the plasma concentration after chronic use.

Potential mechanisms of toxicity

HCQ binds strongly to melanin in the RPE and uvea, and is therefore highly concentrated in these tissues—up to 10,000 times the plasma concentration after chronic use. A primary mechanism of action for HCQ is that it interferes with lysosomal function, specifically autophagy. It interferes with the ability of RPE cells to digest photoreceptor residue, leading to accumulation in lysosomes. Oxidation of the lysosomal product results in lipofuscin formation; its accumulation causes RPE dysfunction.

While the lysosomal toxicity pathway is heavily studied, another proposed toxicity pathway involves the visual cycle. Researchers in Australia and China reported that human organic anion transporting polypeptide 1A2 (OATP1A2) is involved in the uptake of all-trans-retinol (at-ROL) in the RPE. The same researchers also found HCQ to be an inhibitor of at-ROL uptake by OATP1A2. Excess at-ROL accumulation is then converted to lipofuscin. Progressive lipofuscin formation leads to continued lysosomal dysfunction and photoreceptor degeneration. The long half-life of HCQ (40 to 60 days) and high concentration in the RPE cells can result in progressive retinopathy long after drug cessation.

Protecting HCQ-damaged RPE cells

Ruihui Zhang, PhD, and colleagues not-

Figure 2. Spectral-domain optical coherence tomography at diagnosis (top row) shows parafoveal and foveal disruption of the ellipsoid zone, as well as retinal pigment epithelium loss in each eye. This finding is consistent with the beginnings of the severe stage of hydroxychloroquine retinopathy. In the next two rows, follow-up images three years later demonstrate progressive RPE loss extending perifoveally with overlying cystic changes in the retina.
ed that in-vitro HCQ-exposed RPE cells had close to normal levels of healthy RPE cells when they were treated with salbutamol, an adrenergic beta-2-receptor agonist involved in the protein kinase A (PKA) signaling pathway.

To test the involvement of the PKA pathway, they took these same cells (HCQ-exposed RPE cells + salbutamol) and introduced a PKA inhibitor. The viable RPE cells decreased to levels significantly close to that of RPE cells with HCQ toxicity.

This showed that the cyclic adenosine monophosphate (cAMP)-PKA pathway is involved in the protection of RPE cells. They also suggested that beta-2 adrenergic agonists, such as bronchodilators, could be studied to protect against or possibly treat HCQ retinopathy.

REFERENCES

Center-involved DME

Protocol V lessons on observation for CI-DME

Exploring management options for center-involved diabetic macular edema with good vision.

By Mohamed Ashraf, MD, PhD, and Jennifer K Sun, MD, MPH

Take-home points

» Eyes with center-involved macular edema (CI-DME) and good visual acuity showed similar rates of visual loss at two years whether initially managed with aflibercept, laser or observation. Eyes in the laser and observation groups were given aflibercept if vision worsened during follow-up.

» Two-thirds of eyes in the observation group and three-fourths of eyes in the laser group didn’t receive aflibercept during the study.

» Given the costs and risks associated with interventions, observation without treatment unless visual acuity worsens is a reasonable strategy for eyes with CI-DME and good VA.

Mohamed Ashraf, MD, PhD
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Bios

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DISCLOSURES: Dr. Ashraf has no relevant relationships to disclose.

Dr. Sun reports grants from Jaeb Center during the conduct of the study; grants and nonfinancial support from Optovue, Kalvista, Novo Nordisk, Boehringer Ingelheim and Roche; and non-financial support from Merck, Novartis and Adaptive Sensory Technologies outside the submitted work.

Center-involved macular edema with good vision is a clinical scenario many retina specialists and general ophthalmologists commonly see (Figure 1). However, until recently, the best strategy for managing such patients was unknown.

Before the 2019 publication of the DRCR Retina Network Protocol V, some ophthalmologists treated eyes presenting with central fluid on optical coherence tomography because they worried about the potential for long-term damage that might eventually lead to visual loss. Other ophthalmologists worried about treating patients with excellent vision and minimal symptoms with an invasive ocular procedure despite the inherent risks, such as endophthalmitis.

Laying the foundation for Protocol V

It’s not surprising that good visual acuity and central edema can co-exist given the poor correlation between OCT central subfield thickness (CST) and vision. In the Early Treatment Diabetic Retinopathy Study, a large percentage of eyes at baseline had VA of 20/25 or better; 27 percent in the focal/grid laser group and 40 percent in the observation group. In both groups, only a few eyes lost 5 letters or more at two years of follow-up (40 percent in the observation group and 25 percent in the laser group).

Furthermore, not all fluid results in visual acuity loss, as evidenced by a substantial percentage of eyes in DRCR Retina Network Protocols I and T that maintained vision despite chronic persistent fluid.

Protocol V was a multicenter randomized clinical trial of the DRCR Retina Network that aimed to answer the question of how to best manage eyes with good vision despite CI-DME. The study compared three distinct initial management strategies: intravitreal aflibercept (Eylea, Regeneron Pharmaceuticals); macular focal/grid photo-coagulation; and observation.

Two strategies, observation and laser, involved close follow-up with clearly defined criteria for initiating anti-VEGF therapy if
VA declined consistently or substantially. In eyes with CI-DME and good VA, Protocol V reported no difference in VA loss at two years regardless of treatment strategy. Given the potential complications and costs associated with either anti-VEGF injections or focal/grid laser, observation without treatment unless VA worsens may be a reasonable, cost-effective and safe strategy. Here, we review the clinical implications of the key findings of Protocol V.

**Treatment protocol**

The study had three groups: aflibercept (n=226); observation with aflibercept pro re nata for vision loss during follow-up (n=236); and laser with aflibercept p.r.n. for vision loss during follow-up (n=240). The study had a high completion rate of 92 percent (excluding deaths) at two years.

All patients in the aflibercept group received treatment at baseline and were re-evaluated at each visit for possible re-injection. Injections were continued if the VA worsened or improved by 5 letters or more or if OCT CST changed by 10 percent or more from the previous two injections compared to the current visit. Injections were deferred if VA and CST were stable for two consecutive visits and either 24 weeks had passed since injections were started or if VA was 20/20 or better and CST on OCT was below machine- and gender-based thresholds used in previous studies to detect DME.

Laser group patients received laser photocoagulation (focal/modified grid) at baseline. The observation group received no treatment initially. Both groups received aflibercept if VA decreased more than 10 letters from baseline (approximately 2 lines) at one visit or by 5 to 9 letters (1 to 2 lines) at two consecutive visits. While OCT changes were used to modify follow-up durations, anatomic changes in retinal thickness didn’t determine the initiation of treatment.

**Similar outcomes across groups**

The primary study outcome was a loss of 5 letters or more (approximately 1 line) at two years. The percentage of eyes that met that outcome didn’t differ significantly between the treatment groups: 16, 17 and 19 percent in the aflibercept, laser and observation groups, respectively.

At two years, the mean VA letter score change from baseline also didn’t differ statistically between the groups: +0.9, +0.1 and -0.4 letters. Mean VA at two years was equivalent to 20/20 in each treatment group. In addition, the groups didn’t differ significantly in number of eyes with a 5-letter or more vision loss or gain or a 10-letter or more loss at two years.

Perhaps the only notable difference between the groups was the number of eyes with a VA of 20/20 or better at two years: 77 percent for the aflibercept group vs. 66 percent for observation (p=0.03). However, a similar percentage of eyes (84 to 86 percent) in each of the three groups had a VA of 20/25 or better at two years.

Although the mean one-year change in OCT was significantly greater in the aflibercept group, this difference all but vanished at two years. Aflibercept patients had a rapid decrease in CST by eight weeks, which remained stable until the two-year mark. This contrasts with the observation and laser groups, which had a slower but steady decrease in CST from baseline at two years.

**When aflibercept was initiated**

Aflibercept was initiated for vision loss in about a quarter of the eyes in the laser group and about a third in the observation group. The cumulative probability for initiating aflibercept was higher in the observation group than the laser group at both one and

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**Figure 1.** Optical coherence tomography scan of an eye with center-involved macular edema and visual acuity of 20/25.
two years. The median number of aflibercept injections over two years was seven and nine in the laser and observation groups, respectively, vs. eight in the aflibercept group.

**Other observation group outcomes**

Most eyes initially managed with observation didn’t require aflibercept (66 percent, Figure 2). Median VA in this group was 20/20 and 31 percent had spontaneous resolution of DME at two years. Among observation eyes receiving aflibercept, median two-year VA was 20/25, and 70 percent lost less than 1 line of vision.

In the observation group, 19 percent of eyes experienced a 10-letter or more loss at least once for which treatment was initiated. In total, 39 percent of observation eyes had a 5-to-9-letter loss at least once, of which only 32 percent had sustained VA loss on the subsequent visit and required initiation of aflibercept treatment.

In other words, 68 percent of eyes showing an initial 5-to-9-letter loss didn’t require treatment on the subsequent visit, demonstrating the month-to-month variability in VA seen in patients with DME.

Greater OCT thickness at baseline, worse diabetic retinopathy severity (moderately severe nonproliferative DR or worse) and recent (within four months) DME treatment in the non-study eye were all associated with use of aflibercept in the observation group. Age, gender, ethnicity and baseline HbA1c were not associated with an increased probability of receiving aflibercept.

**One approach as good as the other**

The Protocol V results demonstrate that visual outcomes are good with all three initial management strategies of aflibercept, macular laser and observation. However, beginning immediate anti-VEGF therapy in eyes with CI-DME and good vision doesn’t seem to derive any additional benefit. In fact, most eyes in both the laser (75 percent) and observation groups (66 percent) had stable vision and didn’t require rescue aflibercept therapy.

It’s important to highlight that the observation and laser protocols were only the initial strategies adopted. Patients were required to undergo frequent follow-ups and assessments to determine whether their VA was stable or worsening. The study employed a vision-based algorithm to determine when aflibercept treatment was initiated in the laser and observation groups. Hence the treatment of those groups wasn’t with monotherapy, but reflected a strategy of laser or observation for patients who remained stable from baseline and rescue aflibercept therapy for those whose vision worsened over time. Although OCT worsening was used as a parameter to determine follow-up durations, it wasn’t used to determine anti-VEGF treatment initiation.

We must carefully weigh the option of starting therapy vs. a more conservative approach. Aflibercept injections are costly and carry a risk, albeit small, of complications such as endophthalmitis (less than 0.1 percent). Given that observation with p.r.n. aflibercept achieves outcomes similar to immediate aflibercept injections, initial

*Figure 2. Optical coherence tomography scans of two patients with center-involved diabetic macular edema who were observed and didn’t receive treatment over a two-year period (baseline A and C, two-year follow-up B and D). Although both patients had residual edema at the end of their follow-up, they didn’t lose vision and maintained their baseline visual acuity.*
Essay: COVID-19 stress

Guidance for dealing with stresses of the times

Do the right thing, focus on connections, reexamine your life and know that we're going to be OK.

By Andrew Schimel, MD

Take-home points
» Do the right thing for your patients and yourself during this difficult time.
» The most important factor leading to happiness is the quality of relationships with family, friends and our community. Focus on your connections.
» This is an ideal time to reexamine our lives to find more meaning and purpose as we move forward.
» We’re going to be OK.

The 6th Infantry Division of the United States Army holds the unchallenged record for consecutive days of continuous combat, 219 days, on the island of Luzon during World War II. Thousands of soldiers died and even more developed severe post-traumatic stress disorder and were never the same.

My grandfather was a soldier in the 6th during that time. Each night after a brutal day of fighting, the Americans would bomb the Japanese front lines a few hundred yards away. A few exhausted Japanese soldiers would sneak close to the American front line at night to avoid the bombing and catch some sleep, slipping back in the morning before dawn.

One morning my grandfather and his partner climbed out of their foxhole to find a young Japanese soldier sleeping a few yards away. My grandfather's partner held his gun to the Japanese soldier's head, but just as he pulled the trigger, my grandfather kicked his gun away, saving the soldier's life. The Japanese soldier ran back to his side unharmed.

My grandfather went on to live a long, happy and successful life, dying in his mid-nineties surrounded by his 11 grandchildren. He told everyone who would listen that doing the right thing in that most difficult moment to save that young soldier provided every ounce of luck and success he encountered throughout his life.

This is our generational war

There are few moments in life where your response to a situation may define you forever. This COVID-19 crisis is one of them. It is our generational war. We are all facing enormous new and uncomfortable challenges and are attempting to figure out how to cope with the new normal.

Despite our struggles, this is the time to do what's right. You must fight for your patients the best way you know how. Keep them safe in your clinic and provide them with optimal care for their eyes. They'll be grateful and, as a result, you'll feel more emotionally fulfilled.

Through it all, never forget to fight for yourself and your own time. So many people are relying on your health and well-being.

Bio
Dr. Schimel is a partner at the Center For Excellence in Eye Care in Miami and vice president of wellness for the Vit-Buckle Society. He is also an assistant professor at Florida International University, Miami.

Disclosures: Dr. Schimel has no relevant relationships to disclose.
You owe it to them to stay healthy and relaxed. Placing yourself at risk by not getting enough sleep or exercise, or by exposing yourself to an infected patient will likely result in far greater damage than doing the right thing for yourself.

**Relationships matter**

We should be most grateful for our relationships with family, friends and community. In 1938 the Harvard Happiness Study was initiated. The study, which continues to this day, originally followed 724 men throughout their lifetimes to determine what makes people happy. The results definitively showed that the most important contributor to happiness was the quality of relationships in our lives. People who were more socially connected to family, friends and community were significantly happier, physically healthier and lived longer than people who were less connected.

This is the time to nurture your relationships and reach out to your community. In particular, reach out to friends in the medical field who will best understand what you’re going through daily. Open up about your worries, challenges and stresses. While it may seem lonely working through each day covered in our shell of PPE, talking with friends quickly reminds us that we are all going through similar experiences and we’re going to be OK.

**Grieving our losses**

Most physicians are experiencing various levels of grief over losing a way of life that we thought was normal. We think that we took the old way of life for granted. Gone are the days you could comfortably go to your favorite restaurant or out with a large group of friends or family to celebrate an accomplishment.

Many of us are walking slowly through the stages of grief. These include feelings of victimization, anger, frustration and, ultimately, helplessness.

We must help ourselves and each other recognize what we’re going through and reach the final and healthy stage of grief where we discover acceptance. This is where regular communication with close friends and family can help the most.

Helplessness is the most dangerous stage of grief. Research demonstrates this is where we’re at the greatest risk of suicide and addiction.

Each of us has the responsibility to reach out to friends and family to ensure that everyone gets past the feeling of helplessness. Helping others through this difficult time brings significant benefits to both those doing the helping as well as those struggling with helplessness.

**Reaching acceptance**

In the right circumstances, reaching acceptance can lead to peace and allow us to reexamine our own sense of meaning and purpose. We must take time to ourselves to address the following questions:

- Who am I?
- What do I want?
- What’s my purpose?
- What am I grateful for?

By answering these questions, we can redirect our lives in a way that positively affects our work, relationships and future choices.

Take a deep breath and rest assured there’s exciting progress in the search for therapeutics and vaccines to treat and prevent the virus. In all likelihood, we’ll see promising results for a therapeutic treatment and possibly even prevention of the disease in the next few months. More than 100 vaccine candidates are in the works, and we’re already starting to see promising results.

**Bottom line**

Do the right thing. Help yourself and others wade through the stages of grief to acceptance. Reexamine your life and purpose, and solidify your relationships with family, friends and community. Doing so will allow you to not just survive this pandemic, but also thrive as it ends. Above all else, take care of yourself and others.
Three-quarters of the top 10 shared health stories from 2018 were misleading or contained false information. Moreover, false news is 70 percent more likely to be retweeted than factual statements, and online content with accurate medical information takes six times longer to reach 1,500 people compared to falsehoods.

As anyone who has surveyed online social media content knows, since the beginning of the COVID-19 pandemic there has been an alarming increase in distorted or inaccurate postings that directly threaten the validity of medical communications.

Problematically, this creates an adversarial environment for practice promotion and brand building online and can hurt patients with serious consequences. One analysis found that more than 800 people worldwide died and thousands more were hospitalized in early 2020 because of unfounded online claims that ingesting highly concentrated alcohol would kill the novel coronavirus.

### Misinformation, disinformation and propaganda

Before moving further, we should briefly define commonly misused terms. Misinformation is false information that’s spread unintentionally and contrasts with disinformation, which involves untrue claims constructed with deception and intended to mislead. Propaganda is the use of disinformation to promote a particular political viewpoint.

While disinformation and propaganda remain vile anachronisms to the spirit of medical knowledge, misinformation is the most difficult to detect and has proven to be most harmful to medical content since it usually contains some elements of truth.

### How do we combat misinformation?

To deploy an effective strategy against online misinformation, it’s important to recognize that the main limitation of medical content found on social media is a lack of quality control and reliability.

First, identify content that’s unreferenced, incomplete or informal as possibly untrue. While evidence-based medicine devalues anecdotal reports, social media postings tend to over-emphasize these individual accounts as representative of collective medical knowledge. Identify these posts and don’t propagate or share content if it fails your scrutiny.

Second, ensure the content that you post and share is subject to quality control. Verify the content you post from multiple sources and, whenever possible, reference it when appropriate or when providing recommendations.

As a medical professional posting on social media, your opinion should have the jurisprudence of the best available evidence.

**Quotable**

As a medical professional posting on social media, your opinion should have the jurisprudence of the best available evidence.

**Bio**

Dr. Almeida is a vitreo-retinal surgeon at Erie Retinal Surgery in Erie, Pa.

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

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- Email: drpa@pm.me

**REFERENCES**

As we continue to try to function in a pandemic, it’s important to maintain an awareness of various billing rules to avoid a loss of revenue. If you take a moment to review your claim payments, you might notice less reimbursement than you’d expected on some services. If the claim is otherwise coded correctly, you have likely encountered a Multiple Procedure Payment Reduction (MPPR).

How MPPR came about

The background of the MPPR is found on the Centers for Medicare and Medicaid Services website fact sheet. The article explains the Medicare Physician Fee Schedule proposed rule for 2007 includes proposals to implement two provisions of the Deficit Reduction Act of 2005 that affect payment for imaging services. The first provision addresses payment for certain multiple imaging procedures, with full payment for the first procedure but a 25-percent reduction in payment for additional imaging procedures furnished on contiguous body parts during the same session.

CMS explains that because many services have overlapping components, Medicare is attempting to avoid “duplication of payment” when multiple images of contiguous body parts are taken in a single session. The solution to “duplication of payment” is a reduction in payment for the technical component of the service. The rule doesn’t affect the professional component payment. The list of tests subject to MPPR includes many that are common in a retina clinic (Box): ultrasound, imaging and visual fields.

(Continued on page 46)
Geographic atrophy secondary to age-related macular degeneration is a well-known unmet need, and the stakes have been raised as potential treatments for GA move through the pipeline. One of the most advanced candidates is pegcetacoplan, once known as APL-2 (Apellis Pharmaceuticals), a complement inhibitor now in two Phase III clinical trials, DERBY and OAKS.

But a post-hoc analysis of data from the Phase II FILLY trial has gained recent attention. SriniVas Sadda, MD, lead investigator of the post-hoc analysis, recently reported that pegcetacoplan reduced the rate of progression from early stage, or nascent, GA to full-blown GA by about 40 percent compared to sham.1

Pegcetacoplan is a synthetic cyclic peptide conjugated to a polyethylene glycol polymer. It targets C3, a complement factor that has been implicated in AMD. The Food and Drug Administration in 2018 granted it fast-track designation for GA.

Here, Dr. Sadda, president and chief scientific officer of the Doheny Eye Institute in Los Angeles, answers questions about the post-hoc analysis of the FILLY trial. The study was supported in part by Apellis.

**Q: What role does the complement pathway play in geographic atrophy?**

A: The complement proteins C3, C5 and the membrane attack complex (MAC) have been found in the eyes of AMD patients, and particularly in drusen.

Genetic evidence also supports the role of complement proteins in AMD. Complement factor II (CFH) is a regulator of the complement system, and different polymorphisms of the CFH gene are clearly associated with increased risk of AMD. Others, such as C3 and C2, also have variants that increase the risk for AMD and advanced AMD. Some AMD patients have higher serum levels of complement activation products as well. C3 is of particular interest because preclinical studies have shown it may be associated with deposits below the retinal pigment epithelium and even RPE atrophy.

**Q: What was the rationale for the post-hoc analysis?**

A: The goal was to see if pegcetacoplan could have any impact on the progression of macular degeneration outside the GA lesion. It focused on nascent GA, but it also evaluated progression from drusen to nascent GA, also termed incomplete retinal pigment epithelium and outer retinal atrophy (iRORA), or complete atrophy.

Few patients progress from drusen to atrophy in 18 months, but the study population showed a hint of progression events after six months. The sham group seemed to continue to progress after six months, whereas the pegcetacoplan patients stabilized, but the numbers were small.

It was important to determine if the treatment had any positive impact in areas outside the atrophy, which could suggest that the possibility of earlier intervention warrants further exploration.

**Q: How does pegcetacoplan target the C3 pathway?**

A: It specifically inhibits cleavage of C3 into its subproducts, C3a and C3b. It’s an attractive target because, regardless of how complement is activated, pegcetacoplan in essence shuts down the downstream pathway.

The complement cascade has been divided into three major events known as the three A’s: activation followed by amplification, which is a feedback loop that...
amplifies complement, and then the attack that destroys tissue. Disrupting C3 cleavage blocks all downstream activity regardless of the pathway.

**What’s the most significant finding of the post-hoc analysis?**

This was a small study cohort: 42 patients from the monthly pegcetacoplan group and 69 sham patients who completed 12 months of the study receiving all injections and didn’t develop exudative AMD. It should be emphasized that the findings are for hypothesis generation and need to be confirmed in an appropriately powered randomized prospective study. Fifty percent of the pegcetacoplan-treated group demonstrated nascent or full GA vs. 81.8 percent of the sham group (p=0.02). Also, progression from large drusen to nascent GA or GA at 12 months occurred in 22.6 percent of the treatment group vs. 33.3 percent of sham (p=0.31). Overall, paralleling the primary results of the study that showed that pegcetacoplan slowed the progression of GA, this analysis suggested that it also slowed progression from nascent GA to complete atrophy.

**How might the findings inform the DERBY and OAKS trials?**

The primary outcome of FILLY was based on measuring atrophy with fundus autofluorescence. The good news is that DERBY and OAKS are collecting optical coherence tomography scans as well. This may provide an opportunity to determine if the post-hoc FILLY findings can be confirmed in a larger study.

**REFERENCE**


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**Protocol V lessons on observation for center-involved DME**

(Continued from page 40)

observation in eyes with center-involved DME and good vision seems reasonable.

**REFERENCES**


**CODING COMMENTARY**

**Why was your test payment cut?**

(Continued from page 44)

Where it gets confusing

Since 2013 Medicare has reduced the technical component of second and subsequent ophthalmic tests by 20 percent when more than one eligible diagnostic test is performed on the same day. The professional component of the test is paid in full for each test. Thus, if you perform fundus photography (92250) and fluorescein angiography (92235) on the same day, the technical component of photography will be reduced by 20 percent, or about $4.

Things can become confusing when one test is bilateral and another unilateral, such as a B-scan on one eye (unilateral test payment) and fundus photography both eyes (bilateral payment). One B-scan is paid in full while the second B-scan and the photos are subject to the 20-percent technical component reduction, or about $8 total.

Although you can avoid the reduction by scheduling testing on different dates of service, this is generally not a viable strategy. Costs associated with bringing the patient back another day far exceed the MPPR payment reduction.

The most important point is that you have an understanding of how you are (and are not) getting paid. You (or your billing staff) didn’t make an error; the reduction is built into the Medicare manual.

**REFERENCE**

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

The data below reflect the adverse events observed in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 250 patients with macular edema following RVO; and in 251 patients with diabetic macular edema treated with LUCENTIS in 250 patients with DME and/or DR at baseline. (See Clinical Studies (14.1-4) in the full prescribing information.)

Safety data were consistent with trends in adverse events observed in patients treated with LUCENTIS in previous controlled clinical trials. Adverse events in patients not significantly affected by blinding procedures.

Table 1: Adverse Reactions in LUCENTIS-Treated Patients Compared to the Control Group

<table>
<thead>
<tr>
<th>Event</th>
<th>LUCENTIS (n=440)</th>
<th>Control (n=441)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye pain</td>
<td>10% (44)</td>
<td>10% (44)</td>
<td>1.00</td>
</tr>
<tr>
<td>Vision disorders</td>
<td>11% (49)</td>
<td>11% (49)</td>
<td>1.00</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>18% (79)</td>
<td>24% (79)</td>
<td>0.00</td>
</tr>
<tr>
<td>Visual field loss</td>
<td>13% (61)</td>
<td>16% (61)</td>
<td>0.00</td>
</tr>
<tr>
<td>Visual disturbance or vision blurred</td>
<td>10% (44)</td>
<td>16% (44)</td>
<td>0.00</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>4% (18)</td>
<td>4% (18)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>4% (18)</td>
<td>4% (18)</td>
<td>1.00</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>8% (36)</td>
<td>12% (36)</td>
<td>0.00</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>4% (18)</td>
<td>4% (18)</td>
<td>1.00</td>
</tr>
<tr>
<td>Intraocular hemorrhage</td>
<td>3% (13)</td>
<td>3% (13)</td>
<td>1.00</td>
</tr>
<tr>
<td>Intraocular disorder</td>
<td>2% (9)</td>
<td>2% (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Retinal disorders</td>
<td>1% (4)</td>
<td>1% (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>11% (49)</td>
<td>15% (49)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

6.3 Immune responses
As with all therapeutic proteins, there is a potential for immune response to ranibizumab, which is a recombinant humanized monoclonal antibody. The percentage of patients whose last test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assay.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%–5% in the neovascular AMD studies and 0%–8% in the diabetic macular edema studies.

On the 24th month, antibodies to LUCENTIS were detected in approximately 1%–9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some cases were noted to have no visual or intraocular inflammation and were not observed in patients with DME and/or DR at baseline.

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

Administration to breastfed women
Ranibizumab is not recommended for administration to a nursing woman.

8.2 Data
An extensive developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab for 14 days starting on Day 20 of gestation. On Day 21, doses of 0, 0.125, 0.25, and 0.5 mg/kg were administered. Skeletal abnormalities were observed at 4 weeks post-dose and included clefting of the skull and vertebral column. No adverse effect was observed at the dose of 0.125 mg/kg which resulted in trough exposures equivalent to single eye treatment in humans.

8.3 Lactation
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in breastfed women.

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

8.5 Geriatric Use
In the clinical studies, approximately 7% (2449 of 3237) of patients randomized to treatment with LUCENTIS were 65 years of age and approximately 11% (1644 of 3227) were ≥ 75 years of age. (See Clinical Studies (14.1-4) in the full prescribing information.) No notable differences in efficacy or safety were seen when comparing age groups. Adverse effects did not have a significant effect on systemic exposure.

10 CLINICAL STUDIES
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients with DME at baseline. (See Clinical Studies (14.1-4) in the full prescribing information.)

12 PATIENT COUNSELING INFORMATION
Patients should be informed that due to the findings in the LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek ophthalmic care from a ophthalmologist (see Warnings and Precautions (5.1)).

17.5 Patent Information
LUCENTIS®
[ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
DNA 200
123456
South San Francisco, CA 94080-4995

LUCENTIS® is a registered trademark.
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**INDICATIONS**

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Myopic choroidal neovascularization (mCNV)

**IMPORTANT SAFETY INFORMATION**

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

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

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

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

**REFERENCES:**