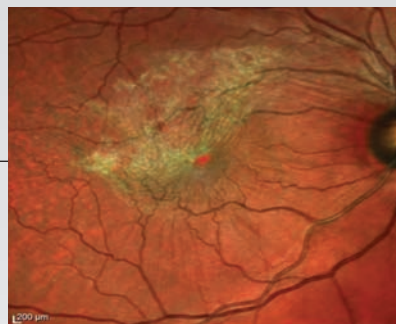
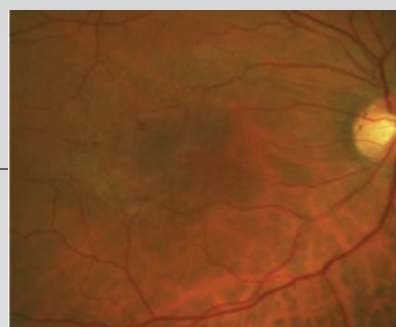


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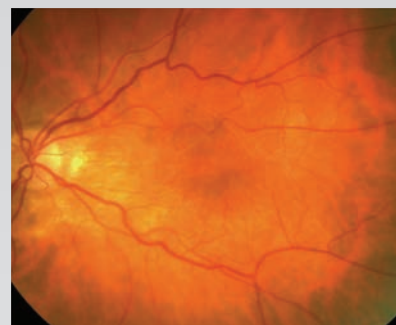
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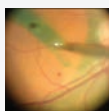
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ONLINE VIDEO

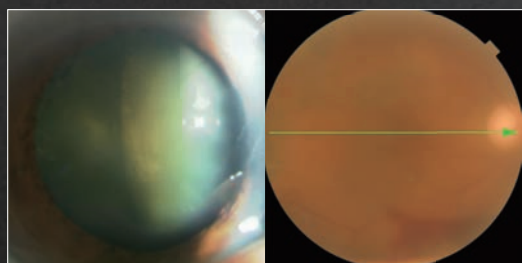


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EDITOR'S PAGE

By Charles C. Wykoff, MD, PhD



Power Athlete, Deep Sleeper

I caved. I succumbed to the marketing of 23andMe, sent them a vial of my saliva and in return for about \$200 was given an entertaining report on my *Health and Ancestry*.

In clinic I find myself talking about gene therapy more and more, what with gene replacement through the Food and Drug Administration's approval of Spark Therapeutics' Luxturna and more potential gene treatments in development, as well as early phase trials employing gene therapy as a platform for drug delivery in wet age-related macular degeneration driven by Adverum Biotechnologies and RegenxBio.

Superficially, the most gratifying finding in my report was that my "muscle composition" was found to be "Common in elite power athletes," although my wife thinks this might be a mistake. I also learned that I am "Likely to consume more" caffeine, and I am "More likely to be a deep sleeper."

More relevant to my daily practice, I learned that I harbor one of the two genetic variants tested for age-related macular degeneration, the Y402H polymorphism in the CFH gene, a genetic locus consistently found to be strongly associated with the development of AMD. This may help explain my family history of AMD. But, the report also informed me that since I am heterozygous, I am "not likely at increased risk of developing AMD." Still, this finding sheds new light on my appreciation for my own vision

Quotable

"While we as a specialty do not routinely offer genetic testing for AMD to our patients, I believe that one day we will."

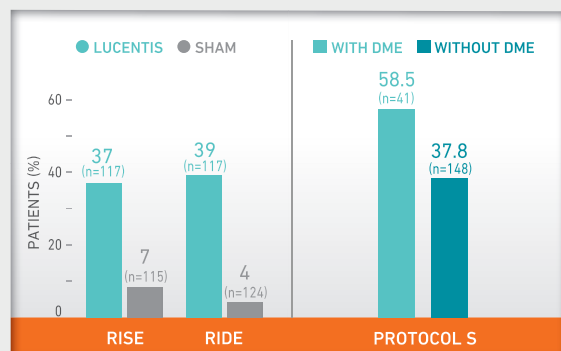
and that of my patients suffering with AMD.

Cumulatively, an estimated three dozen genetic loci account for more than 50 percent of an individual's risk of developing AMD. While we as a specialty do not routinely offer genetic testing for AMD to our patients, I believe that one day we will.

As we continue to develop new pharmaceuticals and devices aimed at improving outcomes and care delivery for patients with AMD, as well detailed by Michael Klufas, MD, and Donald D'Amico, MD, on page 14, I encourage these and future programs to incorporate an exploration of the underlying genetics. We have much yet to learn. ^{RS}

SIGNIFICANT REGRESSION IN DIABETIC RETINOPATHY

≥2-STEP IMPROVEMENTS AT 2 YEARS^{1*}



≥3-STEP IMPROVEMENTS AT 2 YEARS¹:

RISE AND RIDE

- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S

- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).¹

INDICATIONS

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

- Diabetic retinopathy (DR)
- Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg

LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS

- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

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

*The following clinical trials were conducted for the DR & DME indications: **RISE & RIDE**—Two methodologically identical, randomized, double-masked, sham injection-controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. **Protocol S**—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.^{2,3}

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).¹

VEGF, vascular endothelial growth factor.

0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED¹

HELP PATIENTS TURN BACK TO AN EARLIER
STAGE OF DIABETIC RETINOPATHY (DR)¹

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a prefilled syringe. LUCENTIS is the only anti-VEGF approved for DR with or without diabetic macular edema (DME).¹



REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. 2. Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. 3. Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

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LUCENTIS[®]
RANIBIZUMAB INJECTION

LUCENTIS® **RANIBIZUMAB INJECTION**

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

1 INDICATIONS AND USAGE

LUCENTIS is indicated for the treatment of patients with:

- 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 1.3 Diabetic Macular Edema (DME)
- 1.4 Diabetic Retinopathy (DR)
- 1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS

4.1 Ocular or Periorcular Infections

LUCENTIS is contraindicated in patients with ocular or periorcular infections.

4.2 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

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

5.2 Increases in Intraocular Pressure

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

5.3 Thromboembolic Events

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

Neovascular (Wet) Age-Related Macular Degeneration

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

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

Macular Edema Following Retinal Vein Occlusion

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

Diabetic Macular Edema and Diabetic Retinopathy

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

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

5.4 Fatal Events in Patients with DME and DR at baseline

Diabetic Macular Edema and Diabetic Retinopathy

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

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis and Retinal Detachments [see *Warnings and Precautions* (5.1)]
- Increases in Intraocular Pressure [see *Warnings and Precautions* (5.2)]
- Thromboembolic Events [see *Warnings and Precautions* (5.3)]
- Fatal Events in patients with DME and DR at baseline [see *Warnings and Precautions* (5.4)]

6.1 Injection Procedure

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

6.2 Clinical Studies Experience

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

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

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

Ocular Reactions

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

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

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

Non-Ocular Reactions

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

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

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

6.3 Immunogenicity

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

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

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

6.4 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with LUCENTIS.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

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

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

8.3 Females and Males of Reproductive Potential

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

LUCENTIS®
[ranibizumab injection]

Manufactured by:
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A Member of the Roche Group
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South San Francisco, CA
94080-4990

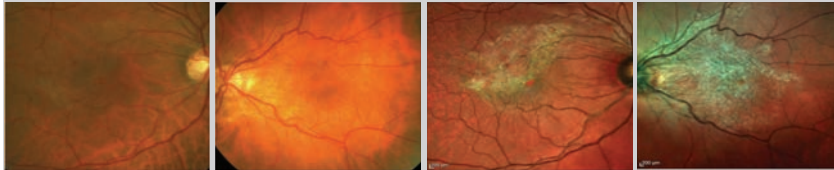
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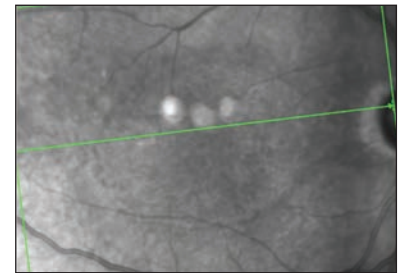
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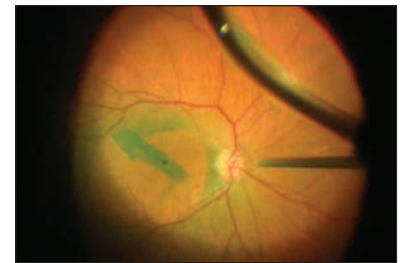


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Does Race for Lucentis Biosimilar Have a Leader?

The Europe-based developer of a Lucentis biosimilar recently released interim Phase III results that it says demonstrate comparable outcomes between the two agents for vision improvements at eight weeks. The company says it is eyeing U.S. approval by 2020.

The news may give Formycon AG of Germany and its Swiss-based licensee, Bioeq IP AG, the advantage, at least for the moment, in the race to develop a biosimilar of Lucentis (ranibizumab, Roche/Genentech). Pfenex has put development of its Lucentis biosimilar candidate on hold. A South Korean company is also developing a Lucentis biosimilar. A biosimilar is a copy-cat of sorts of biological agents, the equivalent to generics of chemical-based agents.

The Formycon-Bioeq candidate, known as FYB201, is the subject of the COLUMBUS-AMD trial for treatment of neovascular age-related macular degeneration. The trial is evaluating patients over 48 weeks of treatment, and the last patients are expected to complete treatment by the end of June, Formycon said in a press release.

Formycon did not release any details of the latest interim findings, but said the confidence interval for improve-

ment of best-corrected visual acuity lies within the predefined equivalence limits, and that the trial has not identified any safety or immunity issues.

Thiemo Schreiber, PhD, of Bioeq, which is conducting the Phase III trial, said the company aims to get approval in the United States in 2020 and in the European Union in 2022—the dates Lucentis comes off patent in the respective jurisdictions.

Pfenex, meanwhile, has shifted gears for its Lucentis biosimilar, PF582. Company Chief Financial Officer Susan Knudson was quoted in April by *BioPharma-Reporter.com* as saying the company would put the development program on hold. Pfenex has had a problem getting PF582 on track since former partner Pfizer pulled out in 2016. Officially, Pfenex says it is still seeking strategic partners for PF582.

Samsung Bioepis of South Korea also has a Lucentis biosimilar, SB11, in Phase III trials, but has not established a time line for the agent.

Lucentis isn't the only anti-VEGF agent attracting biosimilar developers. Alteogen of South Korea says it plans to file an investigational new drug application with the Food and Drug Administration for ALT-L9, a biosimilar of Eylea (afibercept, Regeneron).

IN BRIEF

Optovue received Food and Drug Administration approval for two extensions of its optical coherence tomography angiography platform: AngioAnalytics, a technology that measures blood vessels; and 3D PAR, software that removes three-dimensional projection artifacts from OCTA images. Both are available in the United States.

Should you be doing foot examinations? Researchers from the University of Sheffield in the United Kingdom reported in *Diabetic Medicine* in April that 25 percent of patients with diabetes who had foot exams during their annual retinal screenings received a new diagnosis of distal symmetrical polyneuropathy, while 56.6 percent had a moderate to high risk of developing foot ulcers. 

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Retinal Pathology with Glaucoma

Is macular schisis and serous retinal detachment a coincidence or contribution from the optic nerve head? By Parker Faith, MD, Steven S. Saraf, MD, and Shivali A. Menda, MD

A 59-year-old woman presented to the glaucoma service at our institution for glaucoma suspect evaluation. She was originally evaluated by an outside optometrist who documented intraocular pressures in the mid-30s and advanced optic nerve head cupping in both eyes. She had not been compliant with glaucoma treatment or follow-up for the prior 2.5 years.

Her glaucoma workup demonstrated end-stage angle-closure glaucoma, greater in the right eye than the left. She was also found to have macular retinoschisis and a serous retinal detachment in her right eye, a finding that has been described among glaucoma patients.

Examination Findings

On initial exam, pinhole visual acuity was 20/125 OD and 20/25 OS. IOPs were 39 mmHg OD and 32 mmHg OS. She had a relative afferent pupillary defect in the right eye. Gonioscopy revealed narrow angles in both eyes. Cup-to-disc ratio was 0.95 OD and 0.90 OS, with no optic nerve pit or coloboma. The fundus exam was limited because the patient could not be dilated safely due to her narrow angles. Retinal vessels appeared normal. She was a low myope of about -1 D. She had moderate nuclear sclerotic cataracts in both eyes.

Workup

A 24-2 Humphrey visual field showed severe generalized depression in the right eye and a small central island in the left (Figure 1). Optical coherence tomography of the retinal nerve fiber layer revealed severe thinning in both eyes (Figure

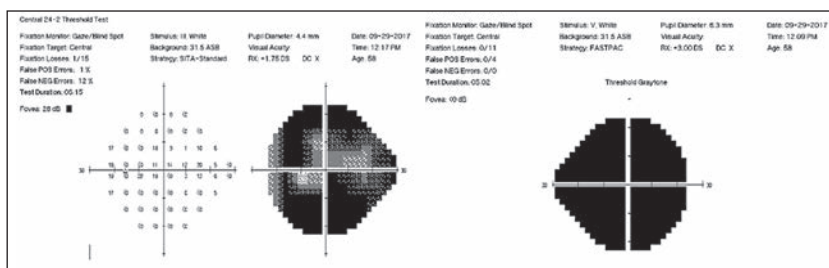


Figure 1. Humphrey visual field 24-2 revealed severe generalized depression in the right eye and a small central island in the left eye.

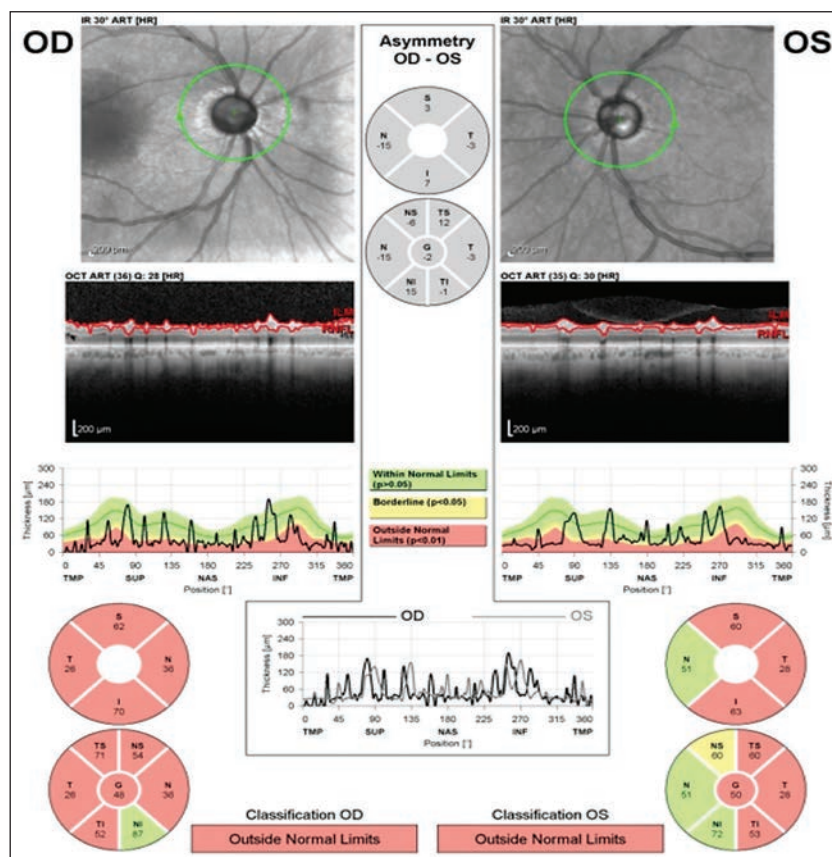


Figure 2. Optical coherence tomography of the retinal nerve fiber layer revealed severe thinning in both eyes.

2). OCT of the macula of the right eye revealed retinoschisis at the level of the outer plexiform layer (OPL), extending from just temporal to the

optic nerve to the fovea. A fovea-involving serous RD appeared deep to the retinoschisis (Figure 3A, page 12). OCT of the left eye was normal.

Diagnosis and Management

Given this patient's advanced glaucoma, we decided to perform combined trabeculectomy and phacoemulsification with intraocular lens placement in both eyes. She had the procedure first in her right eye, then in the left eye five months later. She had an uncomplicated postoperative course, including laser suture lysis and subconjunctival 5-fluorouracil in both eyes. Overall, she experienced good reduction in IOP in both eyes.

Follow-up OCT of the right macula six months after surgery (Figure 3B) revealed reduced but persistent retinoschisis at the level of the OPL with complete resolution of the subretinal fluid. Outer retinal atrophy with disruption of the ellipsoid zone in the area of the resolved detachment was noted. Best corrected visual acuity was 20/70, presumed due to maculopathy from longstanding fluid.

Discussion

The combination of macular retinoschisis and serous detachment has been described in cases of optic disc pits, optic disc colobomas, vitreomacular traction, juvenile retinoschisis and pathologic myopia. More recently, this entity has been associated with glaucoma patients.

A large series described peripapillary retinoschisis in glaucoma patients.¹ Of 372 patients evaluated, 25

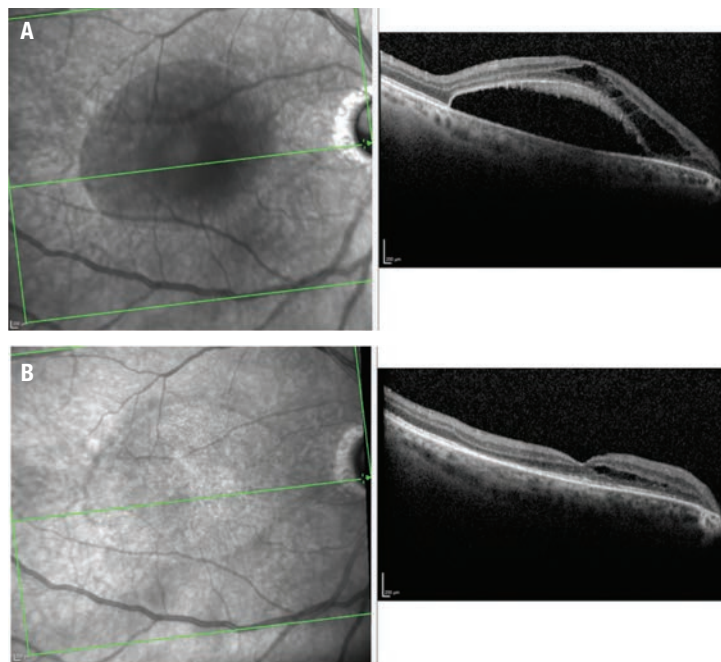


Figure 3. At baseline (A) optical coherence tomography of the macula of the right eye revealed nasal and central retinoschisis and serous subfoveal retinal detachment. At six months postoperatively (B), the subretinal fluid had resolved entirely, but mild persistent nasal retinoschisis appeared at the level of the outer plexiform layer and the subfoveal ellipsoid zone appeared discontinuous.

areas of retinoschisis were identified in 22 patients (5.9 percent). The schisis most commonly involved the retinal nerve fiber layer with variable involvement of deeper retinal layers. This series reported no macular retinoschisis or RD.

Other studies have shown retinoschisis involving the macula. A series of patients with optic nerve cupping and macular schisis, some with serous RD, found that macular fluid resolved in one patient after filtering surgery for uncontrolled glaucoma, and two other patients underwent vitrectomy with intraocular gas with almost total resolution of macular fluid.² Another report described two cases of peripapillary and macular schisis in narrow-angle patients.³ One patient

had resolution of macular schisis with modestly reduced IOP after laser peripheral iridotomy. A case of macular schisis in a patient with primary open-angle glaucoma with postural IOP fluctuations, in which trabeculectomy resulted in resolution of the schisis changes, had also been reported.⁴

Although patients can have two different concomitant pathologies, the trend of finding serous RD associated with optic nerve cupping is illustrated by our report and others. Two similar cases had been described: a case of macular schisis and serous detachment in a patient with angle closure glaucoma, advanced cupping and an IOP of 52

mmHg,⁵ and a case of peripapillary retinal schisis and serous detachment in a patient with POAG and cupping that resulted in spontaneous resolution.⁶

A proposed mechanism for this entity is similar to the mechanism attributed to optic disc pit maculopathy. Liquefied vitreous tracks through a break in the thin tissue of the optic cup and into the retina that can lead to edema, schisis or even serous RD.²

The role of IOP is debatable. In the aforementioned case of macular schisis and detachment, a history of central scotoma that followed an IOP spike up to 52 mmHg supports that IOP may have played a role.⁵ This is further supported by cases where

(Continued on page 40)



Modified ILM Flap for Refractory Holes

A modified approach to internal limiting membrane flaps in eyes with a previous ILM peel.

With Ferhina S. Ali, MD, MPH, and Richard Kaiser, MD

We all dread a macular hole that didn't close on the first try. Wider peels, scraping and/or hydro-dissecting the edge of the hole, and even radial incisions at the refractory hole have yielded generally unsatisfactory results for this unsatisfying subsequent surgery. More recently, autologous transplantation of internal limiting membrane flaps have come into vogue, but this can be technically challenging and frustrating, as anyone who has tried free-flap transplantation surely knows.

Here, Ferhina Ali, MD, MPH, and Richard Kaiser, MD, from Wills Eye Hospital share a modified approach to ILM flaps in eyes with a previous ILM peel.

A Modified Hinged Flap

They favor the use of a flap hinged at the edge of the prior peel. They initiate this subsequent peel nasally to create a thin strip of ILM (*Figure 1*) that is peeled to a temporal hinge, where the strip of peeled ILM is laid over the hole (*Figure 2*).

A temporal (rather than nasal) hinge helps minimize mispositioning of the flap during air-fluid exchange. If a hinged flap is unobtainable, a free flap from eccentric ILM is then harvested, but this approach can be more technically

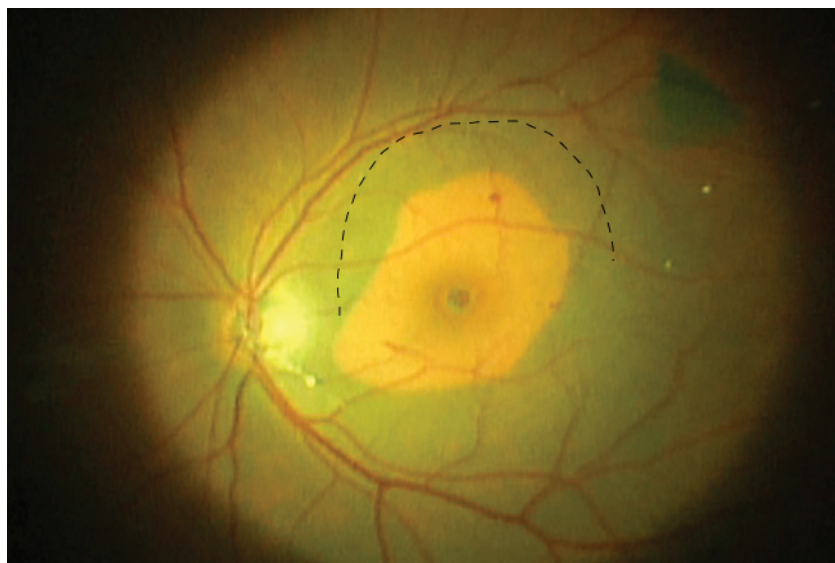


Figure 1. Intraoperative photograph of a persistent macular hole. The dotted lines indicate a peel initiated nasally to temporally to create a temporally hinged flap.



Figure 2. A multilayered temporally hinged internal limiting membrane flap.

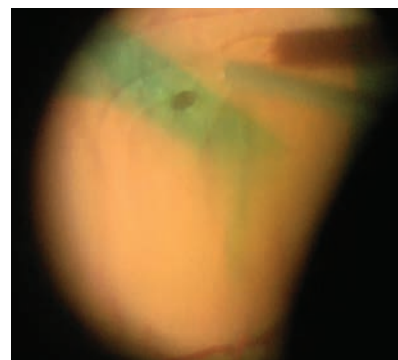


Figure 3. Viscoelastic is injected over the flap using a soft-tipped cannula.

challenging. The free flap can be difficult to release from the forceps over the hole and to keep in place during air-fluid exchange.

Viscoelastic to Maintain Flap

Drs. Ali and Kaiser inject viscoelastic with a soft-tipped cannula over the flap to tamponade the flap (hinged or free) in position. High magnification allows positioning of

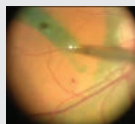
the cannula directly over the flap to mitigate the tendency for viscoelastic to disperse throughout the fluid-filled vitreous cavity (*Figure 3*).

A combination dispersive and cohesive viscoelastic such as Amvisc Plus (Bausch + Lomb) that has high viscosity, high molecular weight, increased surface tension, and adheres well to tissue surfaces
(Continued on page 46)

View the Video

Watch as Drs. Ali and Kaiser successfully repair a refractory macular hole with their modified internal limiting membrane flap technique. Available at:

http://bit.ly/RS_VideoPearl_006



TARGETING UNMET NEEDS IN nAMD TREATMENT

A look at longer-acting anti-VEGF agents, sustained-release delivery, gene therapy and novel molecules in development.

By Michael A. Klufas, MD, and Donald J. D'Amico, MD

Anti-VEGF medications have been revolutionary for the treatment of neovascular, or exudative, age-related macular degeneration, but unmet needs continue. First, intravitreal injections require frequent and indefinite evaluations, with a particularly high burden during the first two years of treatment.¹ Second, current treatments have a short duration of effect. Third, despite robust response and visual gains in many patients, up to 30 percent may continue to lose vision from baseline due to inadequate choroidal neovascularization response, progression of atrophy² or subretinal fibrosis and scar formation. Finally, with long-term follow-up, more than half of patients may have vision worse than 20/40, which may limit their daily activities despite anti-VEGF treatment.³

To address these unmet needs, significant research into improving outcomes in neovascular AMD continues. Current treatments under investigation include new, longer-acting anti-VEGF agents, sustained-delivery systems, gene therapy and molecules targeting novel angiogenesis checkpoints. This article highlights a few of the most promising approaches currently under investigation.

Longer-Acting Anti-VEGF Drugs

Newer anti-VEGF agents are under investigation that may require less frequent dosing, including brolucizumab (RTH258, Novartis)⁴ and abicipar pegol (Allergan and Molecular Partners).⁵

• **Brolucizumab.** This humanized, single-chain antibody of 26 kDa, which is a smaller molecule

than ranibizumab (48k Da) and aflibercept (115 kDa), has a high affinity for VEGF (*Table*).⁴ The molecular properties, including its small size, lead to a fast systemic clearance and ability to deliver a high molar content in a 0.05-cc intravitreal injection volume. The multicenter Phase III HAWK and HARRIER trials compared intravitreal aflibercept (Eylea, Regeneron) 2 mg to intravitreal brolucizumab 3 mg and 6 mg in more than 1,800 patients.

After three monthly loading doses, the 6-mg brolucizumab group met the primary endpoint of non-inferiority to aflibercept every eight weeks as measured by mean change in best-corrected visual acuity from baseline to week 48. In the HARRIER and HAWK trials, 52 percent and 57 percent of patients, respectively, were maintained at a 12-week

dosing interval after initial monthly loading doses through week 48. Intravitreal brolucizumab was well tolerated, and the rate of ocular and non-ocular adverse events was comparable to aflibercept.

ABOUT THE AUTHORS



Dr. Klufas is an assistant professor of ophthalmology at Thomas Jefferson University and is with the Retina Service of Wills Eye Hospital, Philadelphia.



Dr. D'Amico is the John Milton McLean Professor and chairman, Weill Cornell Medicine ophthalmologist-in-chief, New York-Presbyterian/Weill Cornell, New York.

DISCLOSURES: Dr. Klufas is a consultant to Allergan and Genentech, a speaker for Genentech and receives research funding from Novartis.

Dr. D'Amico is a consultant for Alcon/Novartis and PanOptica.

TABLE. Molecular Properties of Anti-VEGF Agents

Agent	Bevacizumab (Avastin, Roche/Genentech) ¹	Ranibizumab (Lucentis, Roche/Genentech) ¹	Aflibercept (Eylea, Regeneron) ¹	Brolucizumab (Novartis) ²
Format	Full antibody (IgG1)	Monoclonal humanized antibody fragment	VEGF receptor 1/2-Fc fusion protein	Short-chain variable fragment
Molecular structure				
Molecular Weight	149 kDa	48 kDa	115 kDa	26 kDa
Clinical dose for nAMD	1.25 mg (off-label use)	0.5 mg	2 mg	6 mg
Equivalent molar dose ³	0.8	Reference	1.7 to 2	22

1: Semeraro F, Morescalchi F, Duse S, Parmeggiani F, Gambicorti E, Costagliola C. Aflibercept in wet AMD: specific role and optimal use. *Drug Des Devel Ther*. 2013;7:711-722.

2: Escher D. Single-chain antibody fragments in ophthalmology. Paper presented at: 15th EURETINA Conference; September 17, 2015; Nice, France.

3: Holz F. Results from two phase II studies evaluating safety and efficacy of RTH258, a single-chain anti-VEGF antibody fragment in patients with neovascular AMD. Oral presentation at: 15th EURETINA Conference; September 19, 2015; Nice, France. Images courtesy Novartis.

• **Abicipar pegol.** This is a DARPIn, or designed ankyrin repeat protein (*Figure 1, page 16*)—a novel class of synthetic, small-binding proteins with high affinity and specificity that blocks all isoforms of VEGF-A, along with very long half-life of up to two weeks.⁵ In the Phase II REACH studies, intravitreal abicipar 2 mg monthly for three loading doses outperformed monthly intravitreal ranibizumab 0.5 mg (Lucentis, Roche/Genentech) at a 20-week endpoint, with the abicipar group gaining 9 letters and the ranibizumab group gaining 4.7 letters.

Of note, the gain of vision with ranibizumab in previous trials with monthly dosing, including MARINA, ANCHOR and CATT, showed a vision gain of 6 to 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. In the Phase II trial of abicipar, 10 percent of patients experienced episodes of ocular inflammation, which has also been observed with aflibercept in clinical practice and may be reduced with improved formulation of abicipar and purification during the manufacturing process. Two Phase

III trials, CEDAR and SEQUIOA, comparing abicipar 2 mg dosed at eight and 12 weeks and ranibizumab at four weeks are now fully enrolled with results expected later in the year.

Sustained-delivery Treatments

Another strategy to address the treatment burden of frequent anti-VEGF injections is sustained delivery. Encapsulated cell technology, such as the NT-503 vitreous implant (Neurotech), with encapsulated retinal pigment epithelium cells that produce a vascular endothelial growth factor receptor for up to two years, have been investigated. Other, more recent sustained-delivery implants include the ranibizumab Port Delivery System (RPDS, Roche/

Genentech) and the Posterior MicroPump Drug Delivery System (Replenish Inc.).⁶ Another sustained-release technology is GB-102 sunitinib maleate (GrayBug Vision), a non-inflammatory biodegradable polymer that is injected via a 27- or 29-gauge needle and inhibits VEGF-A and platelet-derived growth factor (PDGF).

RPDS is a non-biodegradable intraocular reservoir that is inserted via a 3.2-mm pars plana incision in the operating room. It allows delivery of concentrated ranibizumab over four to six months (*Figure 2, page 17*).⁷ The 50- μ l reservoir can be refilled in the office with a proprietary syringe to access the device. Phase I results have shown a vision gain comparable to monthly

Take-home Point

Management of neovascular age-related macular degeneration has greatly evolved, and the findings from initial studies of anti-VEGF agents resulting in vision gain remain seminal and noteworthy. The standard of care continues to be individualized monotherapy with pan-vascular endothelial growth factor-A inhibitors. However, indefinite and frequent treatment has prompted the search for improved therapeutics including newer VEGF blockers with increased durability, sustained-delivery approaches and novel therapeutic targets in the angiogenesis cascade. Recent negative results with antiplatelet-derived growth factor targets suggest that anti-VEGF monotherapy has set a very high standard.

intravitreal ranibizumab; however, some cases of postoperative vitreous hemorrhage have been reported.

The surgical procedure has been modified to deliver laser treatment to the bed of the scleral incision during insertion to decrease the incidence of post-procedure vitreous hemorrhage. The Phase II LADDER trial is currently fully enrolled with approximately 220 patients at 45 sites randomized to three doses of ranibizumab in the RPDS device (10 mg/mL, 40 mg/mL, 100 mg/mL) vs. monthly ranibizumab. The primary outcome is timing to first refill of the RPDS.

Gene Therapy

Gene therapy for RPE65 mutations in Leber congenital amaurosis (LCA) recently received Food and Drug Administration approval,⁸ and interest in this type of therapy for treatment of nAMD continues to grow.⁹ Gene therapy uses a viral vector as conduit for transferring genes that instruct the host cells to produce therapeutic proteins that bind VEGF. It offers the promise of long-term, durable expression of anti-VEGF proteins after a single administration.

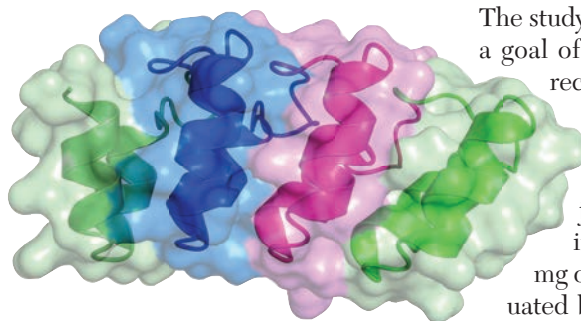


Figure 1. Each ankyrin repeat domain of the DARPin is shown in a different color. The outer green colors are considered “cap” domains, while the blue and pink represent two internal domains. The concave surface at the bottom of the DARPin forms the binding surface for vascular endothelial growth factor A. (Image courtesy Allergan)

• **AVA-101 (Adverum Biotechnologies Inc.).** This adenoviral-associated virus (AAV) vector has been delivered via pars plana vitrectomy and subretinal injection. It produces sFLT-1, a tyrosine kinase inhibitor that binds VEGF.¹⁰ Phase II data of 32 patients (21 treatment, 11 control), showed a wide distribution of outcomes, including a subset of patients who showed signs of encouraging activity.¹¹ The median number of rescue injections using the protocol-specified re-treatment regimen was two in AVA-101-treated subjects compared with four in the control group.

• **RGX-314 (RegenxBio Inc.).** An investigational AAV8 gene therapy being developed for patients with nAMD, RGX-314 contains a transgene that leads to the production of anti-VEGF fab protein that exhibits anti-VEGF activity similar to ranibizumab. A Phase I multiple cohort, dose-escalation study to evaluate the safety and tolerability of gene therapy with RGX-314 in patients with nAMD is underway. The primary endpoint is safety of RGX-314 through week 26 with incidence of ocular and non-ocular adverse events (AEs) and serious AEs. The study is currently enrolling with a goal of 18 participants who will

receive three dose cohorts of RGX-314 (3 x 10⁹ GC/eye, 1 x 10¹⁰ GC/eye and 6 x 10¹⁰ GC/eye). Subjects with nAMD receive intravitreal ranibizumab 0.5 mg on day one and will be evaluated by spectral-domain optical coherence tomography one week later to confirm anatomic response to initial anti-VEGF activity, and then at week two will receive a single dose of

RGX-314 via pars plana vitrectomy with a subretinal injection.

Novel Angiogenesis Targets

Another therapeutic approach is targeting other parts of the angiogenesis cascade beyond VEGF, which are numerous and include targets such as growth factor, interleukin, angiopoietin and matrix metalloproteinases.

Combination Therapies

The much-anticipated results of combination therapy with inhibitors of PDGF, including Fovista (Ophthotech Corporation) and rinucumab (Regeneron) in combination with anti-VEGF therapy, have failed to show superiority over anti-VEGF alone.¹²

• **Squalamine.** Squalamine lactate 0.2% (Ohr Pharmaceuticals) is a small-molecule agent that inhibits not only anti-VEGF but also PDGF and fibroblast growth factor through the modulation of the protein calmodulin.¹³ While intravenous squalamine has been poorly tolerated, the exploratory Phase II IMPACT trial suggested topical squalamine b.i.d. provided a 65 percent added benefit to ranibizumab p.r.n. However, given the disappointing results of intravitreal PDGF inhibition, the sponsor does not plan to continue with a Phase III trial at this time.

Current combination studies are investigating compounds that inhibit anti-VEGF and downregulate angiopoietin 2. They include the bispecific antibody RG7116 (Roche/Genentech) and nesvacumab (Regeneron) co-administered with aflibercept.

• **Targeted immunotherapy.** In this novel approach, vascular endothelial cells and macrophages express tissue factor (TF) in choroidal neovascularization but not normal micro-

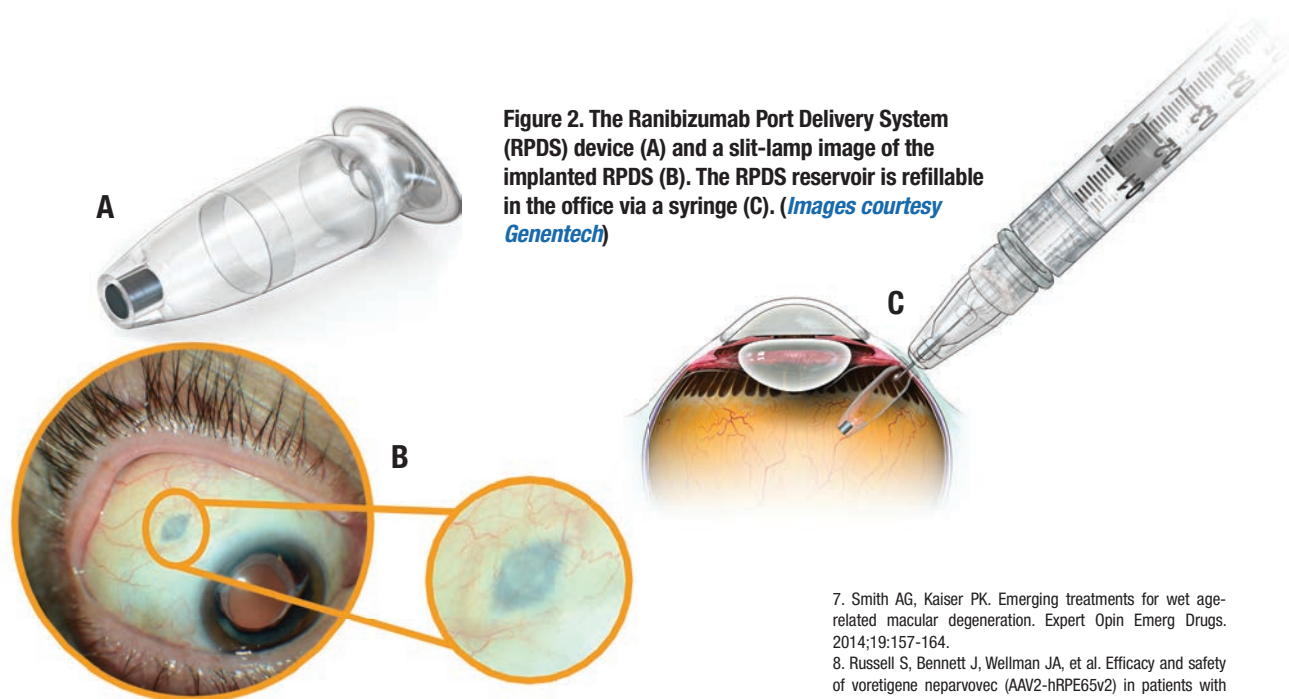


Figure 2. The Ranibizumab Port Delivery System (RPDS) device (A) and a slit-lamp image of the implanted RPDS (B). The RPDS reservoir is refillable in the office via a syringe (C). (Images courtesy Genentech)

vasculature.¹⁴ ICON-1 (Iconic Therapeutics) is a recombinant human fusion protein (composed of factor VII and antibody) that binds TF. Binding of ICON-1 then triggers an endogenous cytotoxic effect via natural killer cells to regress and destroy choroidal neovascularization. Phase II EMERGE results have suggested that intravitreal ICON-1 in combination with ranibizumab enhances the durability but not the efficacy of ranibizumab monotherapy with less re-treatment and longer time to re-treatment.¹⁵

What About Dry AMD?

It is important to note that significant advances in the treatment of dry or nonexudative AMD also represent an unmet clinical need. Although there is a clear and highly significant genetic association with AMD and complement factor H,¹⁶ attempts to turn this into a successful therapeutic target have not

materialized.¹⁷ Failed efforts have included targeting factor D,¹⁸ but clinical trials are currently underway investigating C5 inhibition (Zimura, Ophthotech), C3 inhibition (APL-2, Apellis) and cell therapies, including stem-cell suspensions (Astellas Pharma) and polarized parylene monolayers.¹⁹ 

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ERM PATHOGENESIS: THREE THEORIES SUGGEST DEFECTS OF VITREOUS AND ILM

Controversy surrounds the causes of idiopathic epiretinal membrane, but the dominant theories are not necessarily mutually exclusive.

Jeffrey G. Gross, MD

Several names have emerged in the literature to describe the varying severities of idiopathic or primary epiretinal membrane. They include cellophane maculopathy, preretinal membrane, preretinal fibrosis and macular pucker. The term epiretinal membrane is the most common in the medical lexicon and best describes the entire spectrum of this condition.

ERM is a very common condition, occurring in approximately 6 to 11.8 percent of the U.S. population, but seniors are at greater risk; the incidence increases to 15.1 percent in those over age 70.¹⁻³ Simple ERM has been described as a non-contractile membrane on the macula (Grade 1), often referred to as cellophane maculopathy. Complex ERM has been described as ERM creating striae and retinal folding with vision disturbance (Grades 2 and 3), often termed macular pucker or preretinal fibrosis.⁴

The pathogenesis of ERM has been controversial. This article describes three convincing arguments regarding the pathogenesis of ERM based on histologic, imaging and in-

traoperative observations relating to its formation.

Clinical Characteristics

The clinical characteristics of idiopathic ERM are retinal striae and folding, macular pseudohole, progressive contracture and, in rare instances, spontaneous separation (*Figure 1*). The ERM is almost always located in the posterior retina within the vascular arcades.

Even though the membrane may not cover the fovea, vision loss may occur due to the tractional retinal folding that extends into the fovea. The resulting metamorphopsia often creates a clinically significant disturbance in vision. Spontaneous separation is rare, especially

in adults, and seems to be a result of posterior vitreous detachment (PVD) releasing a wrinkled or opacified posterior vitreous membrane or ERM from the retinal surface.⁵ This often results in improved vision, but it can be associated with bothersome premacular floaters.

An age-related PVD may tear, avulse or cause a dehiscence of the internal limiting membrane, allow-

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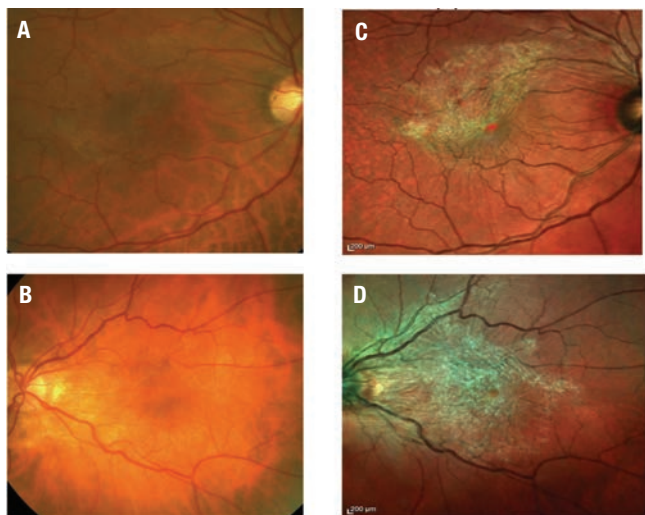


Figure 1. The epiretinal membrane is difficult to discern with fundus photography (A and B), but it can easily be imaged with multicolor scanning ophthalmoscopy (C and D).

ing microglial cells access to the preretinal surface. These cells may interact with a segment of retained vitreous cortex cellular membrane on the retinal surface after a vitreoschisis or PVD.

The ERM, anchored to the underlying retina by microglial cells, undergoes contraction that creates the tangential forces that cause retinal folding, leading to macular pucker.

Contracture of the ERM can sometimes create an internal limiting membrane tear that scrolls into a hyperconvoluted edge, leaving a membrane-free retina without striae. This edge can easily be imaged with multicolor scanning ophthalmoscopy and correlated with SD-OCT, providing a presurgical landmark useful to peel the ERM and ILM en bloc.

Five Major Cell Types

There are five major morphologically distinguishable cells types that

have been identified in pathologic specimens of ERM. They are:

- retinal pigment epithelial cells;
- macrophages;
- fibrocytes;
- fibrous astrocytes; and
- myofibroblast-like cells.

RPE cells create secondary ERM or proliferative vitreoretinopathy and are usually only found in association with retinal tears or retinal detachment. The formation of collagen and the transdifferentiation of cells to those with myofibroblastic properties appear to be the basis for the contractile properties of ERMs.^{6,7}

More recently hyalocytes, often found as resident cells in the posterior vitreous cortex, have been identified as the cells with the greatest potential to develop into myofibroblastic-like cells.⁸

Laminocytes have a morphology similar to hyalocytes and a distinctive laminar arrangement on the ILM

with novel basement membrane production. Pathologist David Snead in the United Kingdom originally described laminocytes as the exclusive cell type in cellophane ERM, and their removal during ILM peeling may account for the success of surgery for ERM, vitreomacular traction syndrome and macular hole.⁹

Theories of ERM Pathogenesis

There are two commonly considered hypotheses and one newer theory, all of which have PVD as the critical event triggering ERM formation. In fact, either partial or complete PVD has been documented in 85 to 90 percent of all cases of macular pucker.^{3,10} ERM-like tissue, possibly opacified and wrinkled posterior hyaloid membrane, has been found in 10 percent of eyes without a PVD. This may explain the phenomenon of spontaneous ERM separation in a small group of patients.¹¹

Theory 1: Microglial Cells Migrate

Robert Foos, MD,¹² originally proposed that retinal microbreaks in the ILM that develop as a result of a PVD allow microglial cells to migrate and spread onto the retinal surface. These cells pass through very tiny pores and then differentiate into fibroglial cells.

Initially described by J.R. Wolter, MD, in 1964,¹³ pores in the human retina were observed in histologic specimens, usually over a small vessel and accompanied by phagocytes. These phagocytes represent

Take-home Point

This article describes convincing arguments about the formation of idiopathic epiretinal membrane. These theories are not necessarily mutually exclusive. An ERM may form as a result of a combination of these processes. An internal limiting membrane dehiscence from a posterior vitreous detachment may allow microglial cells to access the preretinal surface and interact with vitreous cellular membrane, which contains hyalocytes, and/or laminocytes, and transdifferentiates into fibroblastic-like cells that form the cellophane-thin ERM. Retinal folds from ERM contraction create a macular pucker. The ILM can tear and hyperconvoluted scrolling forms an edge easily imaged to aid in surgery.

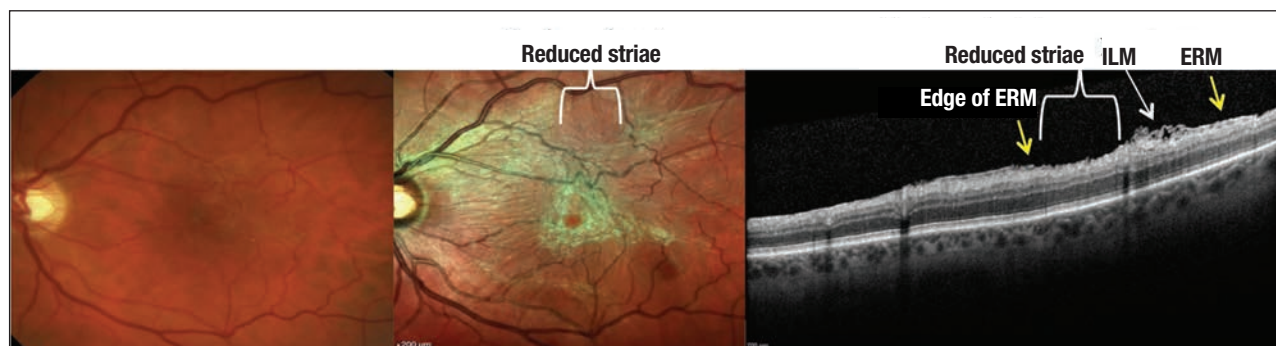


Figure 2. Scrolling of the internal limiting membrane appears adjacent to the retina absent of epiretinal membrane and reduced striae.

glial cells that stretched through the very tiny openings in the ILM, from the retina into the vitreous, or as Dr. Wolter described it, in the manner of a cat going through a small hole.

This appears to be a one-way journey, because these cells have not been seen to migrate in the opposite direction. The migration of these cells through the pores of the ILM may then allow considerable anchorage of the resulting membrane to the underlying retina. This ERM anchorage and contracture forms tangential traction, creating the retinal folding that results in clinically observable striae of complex ERM.

The most common argument against this theory is that microbreaks or pores are rarely observed

in histologic specimens. However, although histologic sections have shown these glial cells as they migrate through the pores, these pores may spontaneously close after glial cells migrate through them.

Theory 2: Segments of Cellular Vitreous Remain on Retinal Surface

Jerry Sebag, MD,¹⁴ refined the theory originally proposed by Norman Jaffe, MD,¹⁵ and Howard Tenenbaum, MD,¹⁶ that a PVD results in segments of cellular vitreous that remain on the retinal surface. In this theory, which Dr. Sebag termed anomalous PVD, vitreous liquefaction without sufficient concurrent vitreoretinal interface dehiscence

allows these segments of the vitreous to remain on the retina despite other portions completely separating from

Imaging of ERM

Diagnosis of the epiretinal membrane is made initially with retinal ophthalmoscopy and confirmed with color photography, fluorescein angiography, multicolor scanning ophthalmoscopy and optical coherence tomography. Multicolor scanning ophthalmoscopy, a recent feature on some OCT devices, provides a very sensitive method to identify ERM and monitor for growth, change or contracture. It can also demonstrate the location of inner limiting membrane scrolling and membrane-free retina adjacent to the ERM.

Membrane-free retina is identified as an area of reduced striae bordered by complex ERM (Figure 2).²⁴ In cases of macular pucker, hyperconvoluted internal limiting membrane occurs between the membrane-free retina on one side and ERM on the opposite side.²⁴

The scrolled ILM creates a floral bouquet pattern on OCT that is strikingly similar to histologic specimens of removed ILM (Figure 3). This scrolled ILM also creates a visible edge that may provide a useful presurgical landmark to facilitate peeling of the ERM and ILM together (Figure 4, page 22).^{22,24}

Interestingly, it appears that ERMs, although possibly induced by defects in the ILM, do not seem to develop over large areas of ILM-free retina.

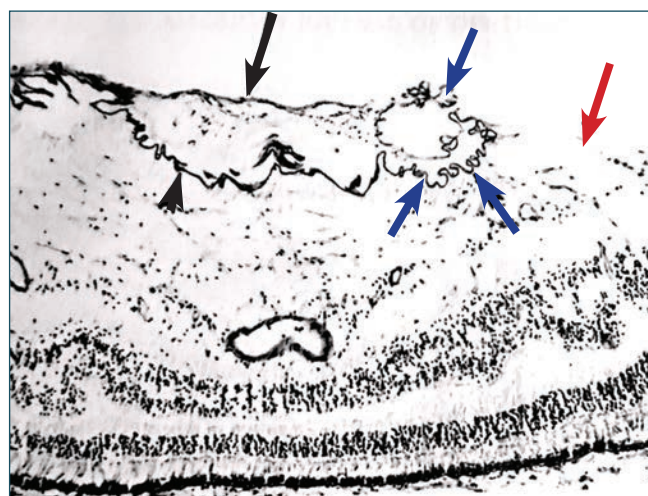
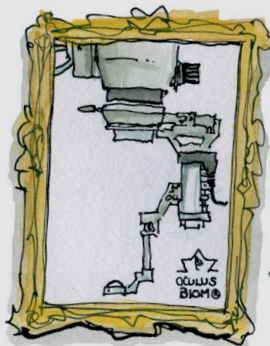


Figure 3. Histology section shows a thick fibroglial epiretinal membrane (black arrow) with wrinkling (arrowhead), scrolling (blue arrows) and a large gap in the internal limiting membrane (red arrow). (Used with permission. Clarkson J et al. *Am J Ophthalmol*. 1977;84:1-17)



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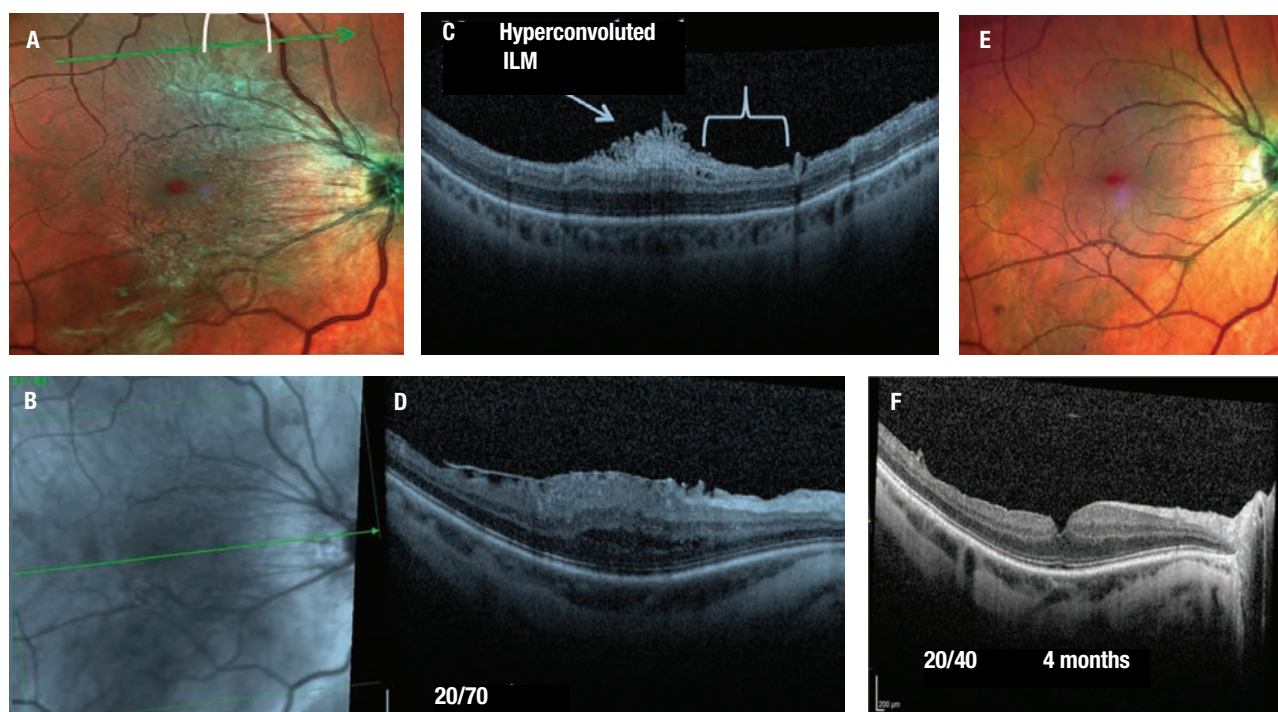


Figure 4. Preoperative multicolor imaging (A) and optical coherence tomography (B, C, D) show hyperconvolution of the internal limiting membrane (arrow) adjacent to membrane-free retina (brackets). Peeling of both the epiretinal membrane and ILM during surgery results in an improved retinal appearance and contour. (E, F)

it.

Segments of vitreous that contain hyalocytes transdifferentiate into myofibroblasts after the PVD leading to ERM formation. A splitting or vitreoschisis has also been identified.¹⁷ Some studies, having failed to identify retained cortical vitreous in the location of future ERM forma-

tion,¹⁸ provide an argument against this theory.

Theory 3: Avulsion Defects

Kirk Packo, MD, based on personal intraoperative observations, has suggested that ERMs may evolve from avulsion defects primarily in the posterior paravascular retina.¹⁹ The ILM is thinnest adjacent to

posterior retinal vessels and avulses during a natural or surgical vitreous separation. ERM formation then results from an upregulation of cytokines caused by this PVD-induced ILM avulsion process. Dr. Packo has observed a lack of indocyanine green staining along the paravascular retina during ERM surgery, supporting this hypothesis.

The argument against this observation is that the very thin ILM in the paravascular retina may not stain with ICG or other stains, and thus the longitudinal area along the vessels may only appear to be absent of ILM.

Other authors have reported this same lack of staining pattern in the paravascular retina in histologic specimens as well.^{20,13} Also, ERM formation does not seem to occur following surgical peeling of ILM, al-

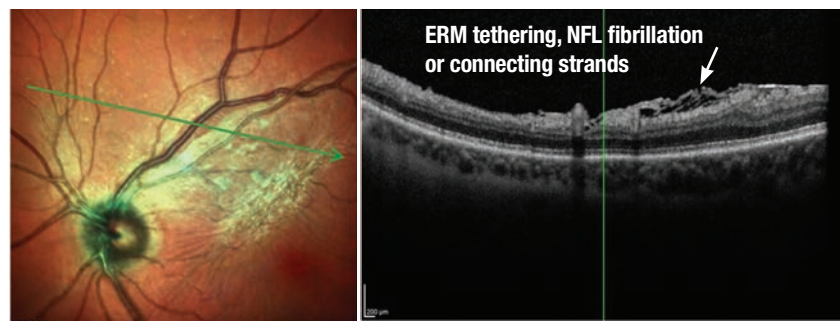


Figure 5. Connecting strands (i.e., epiretinal membrane tethering, nerve fiber layer fibrillation, arrow) along the superotemporal arcade in an eye with ERM and paravascular internal limiting membrane dehiscence.

Figure 6. Multicolor scans show progressive epiretinal membrane contracture (white arrows) in relation to retinal vessels (yellow arrows) with development of an ERM edge (white arrows on optical coherence tomography).

though the removal of the vitreous may deprive the tissue of cellular elements necessary for ERM formation.

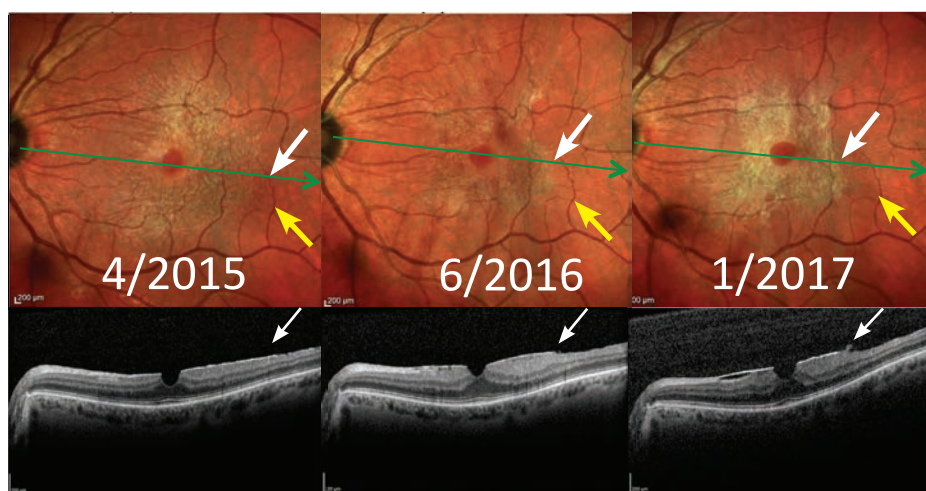
ILM Dehiscence

Gregory Fincham, MRCOphth, has reported on electron microscopy to demonstrate that an ILM dehiscence occurs frequently with age-related PVD, and this delaminated inner ILM layer is the posterior vitreous membrane seen clinically.²¹

Etienne Bovey, MD, has described that a tear, break or detachment of the ILM can occur as a result of a partial perifoveal posterior vitreous separation exerting traction on the ILM.²² According to Dr. Bovey, as the PVD continues, the edge of ILM folds inward toward an ERM present on the retinal surface; eventually the posterior vitreous separates from the ERM.

This tear or avulsion can be seen clinically during chromovitrectomy as a patch of absent ICG staining bordering an arcuate band or edge that is the folded ILM adjacent to the ERM. Histology sections from eyes enucleated for unrelated reasons have demonstrated a similar infolding or hyperconvolution of torn ILM adjacent to an ERM (Figure 3, page 20).²³ Attempting to peel in this unstained area may damage the bare nerve fiber layer.²²

We reported the results of spectral domain optical coherence tomography combined with multicolor im-



aging in eyes with ERM.²⁴ We compared these findings to previously published histologic specimens to suggest that the ripped and scrolled ILM may be caused by the adjacent ERM contracture and only initiated by the PVD (Figure 2, page 20).

Spindle- or oval-shaped ILM dehiscences present in some eyes with ERM, and tangential traction after PVD may also cause corresponding deep lamellar-like excavations or defects in the nerve fiber layer.²⁴ This type of large defect, easily seen in the posterior paravascular retina using multicolor scanning ophthalmoscopy or even upon careful clinical examination, may represent a different pathogenic process because it has also been observed in high myopia without ERM.²⁵

Cynthia Toth, MD, using intraoperative OCT, has described contracting ERM as a cause of tethering or fibrillation of the NFL, also termed connecting strands (Figure 5).²⁶ These connecting strands likely result from ERM contracture causing tractional forces to the NFL, creating a schisis. Interestingly, these connecting strands have been shown to remain temporarily visible on intraoperative OCT just after ERM

peeling, but retract or disappear in the days after ERM peeling.

Progression of ERM

Only 9.3 percent of cellophane membranes have been reported to develop into fibrotic membranes with retinal folds.²⁷ Nearly 29 percent of existing ERMs (both cellophane and fibrotic) and 16.1 percent of the more severe fibrotic ERMs are reported to progress over time. Most are stable and some even regress.

Although growth of the ERM has been observed, it does not typically begin as a small nidus and grow larger. Rather the ERM may begin as a nearly full-sized thin cellophane membrane with indistinct margins. This is possibly created by retained vitreous segments or after vitreoschisis splits the vitreous cortex and leaves a hyalocyte-rich cellular membrane on the retinal surface, after an age-related PVD.

Shoji Kishi, MD, in Japan has described an oval defect in the posterior hyaloid membrane that corresponds to retained membrane in the macula.¹¹ This type of membrane is difficult to image precisely with conventional photography, especially in eyes with cataracts, and it may be

(Continued on page 46)



IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

Adverse Reactions

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

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

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

IMPORTANT SAFETY INFORMATION (CONT'D)

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

Immunogenicity

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

Pediatric Use

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

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

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

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1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis

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

5.2 Permanent decline in visual acuity

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

5.3 Retinal abnormalities

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

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

5.4 Increased intraocular pressure

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

5.5 Expansion of intraocular air bubbles

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

5.6 Cataract

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other products and may not reflect the rates observed in practice.

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

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

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

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

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

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

Immunogenicity

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Lactation

Risk Summary: There is no information regarding the presence of LUXTURN in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURN and any potential adverse effects on the breastfed infant from LUXTURN.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURN on fertility.

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

17 PATIENT COUNSELING INFORMATION

Advise patients and/or their caregivers of the following risks:

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

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

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

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

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

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

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

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SCORE2

LESSONS FOR TREATMENT OF ME DUE TO CRVO OR HRVO

This study provides Level 1 evidence that bevacizumab and aflibercept have similar visual acuity outcomes in patients with macular edema associated with central or hemi-retinal vein occlusion.

By Ingrid U. Scott, MD, MPH

Retinal vein occlusion is the most common retinal vascular disorder after diabetic retinopathy, affecting 1 to 2 percent of individuals older than 40 years^{1,2} and an estimated 16 million people worldwide.³ In patients with RVO, macular edema is the most common cause of decreased vision.^{4,6}

Industry-sponsored Phase III clinical trials have demonstrated the efficacy of monthly intravitreal

ranibizumab⁷ (Lucentis, Roche/Genentech) and monthly aflibercept^{8,9} (Eylea, Regeneron) therapy for the treatment of macular edema associated with central retinal vein occlusion (CRVO). Further, case reports and small clinical trials demonstrated favorable visual outcomes following intravitreal bevacizumab (Avastin, Roche/Genentech) therapy for CRVO-

associated macular edema.¹⁰⁻¹⁴

Ranibizumab and bevacizumab inhibit all isoforms of vascular endothelial growth factor A, and both have demonstrated similar safety and efficacy in the treatment of age-related macular degeneration¹⁵ and diabetic macular edema.¹⁶ Aflibercept, a fusion protein of key domains from both VEGF receptor 1 and VEGF receptor 2, inhibits

not only all VEGF-A isoforms, but also VEGF-B and placental growth factor.¹⁷ In addition to its broader mechanism of action, aflibercept has been reported to have a higher binding affinity than ranibizumab.^{15,17} Bevacizumab repackaged

Take-home Point

The *Study of COmparative Treatments for REtinal Vein Occlusion 2* (SCORE2) investigated the efficacy and safety of intravitreal bevacizumab (Avastin, Roche/Genentech) and aflibercept (Eylea, Regeneron) for the treatment of macular edema secondary to central retinal vein occlusion or hemi-retinal vein occlusion. The study found that monthly bevacizumab was noninferior to monthly aflibercept at six months with respect to visual acuity gains, and both treatment groups demonstrated significant and similar decreases in central subfield thickness. However, the bevacizumab group had a significantly lower proportion of eyes that achieved resolution of macular edema at month six.

ABOUT THE AUTHOR



Dr. Scott is the Jack and Nancy Turner Professor of Ophthalmology and professor of public health sciences at Penn State College of Medicine, Hershey. She serves as chair of the National Eye Institute-funded Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2).

DISCLOSURES: Dr. Scott disclosed serving on the Data and Safety Monitoring Committee for a clinical trial sponsored by Thrombogenics.

at compounding pharmacies into syringes for intravitreal injection is much less costly than aflibercept or ranibizumab.

How SCORE2 Was Designed

The Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2)¹⁸⁻²⁰ was designed to determine if bevacizumab is non-inferior to aflibercept for the treatment of macular edema secondary to CRVO (Figure) or hemi-retinal vein occlusion (HRVO). In addition, SCORE2 compared monthly dosing to treat-and-extend dosing of aflibercept or bevacizumab from six to 12 months with respect to visual acuity and central retinal thickness at month 12 in participants who had a protocol-defined good response after six monthly injections of aflibercept or bevacizumab.

SCORE2 also evaluated the impact of alternative treatment strategies (a different anti-VEGF agent or intravitreal dexamethasone) in eyes that did not have a protocol-defined good response after six monthly injections of aflibercept or bevacizumab. SCORE2's primary results (at six months) will be the focus of this article.

Main eligibility criteria for SCORE2 included:

- best-corrected electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) visual acuity letter score (VALS) between 19 and 73 (approximate Snellen acuity 20/40 to 20/400);
- center-involved macular edema due to CRVO or HRVO on clinical examination; and
- central retinal thickness on spectral-domain optical coherence tomography, defined

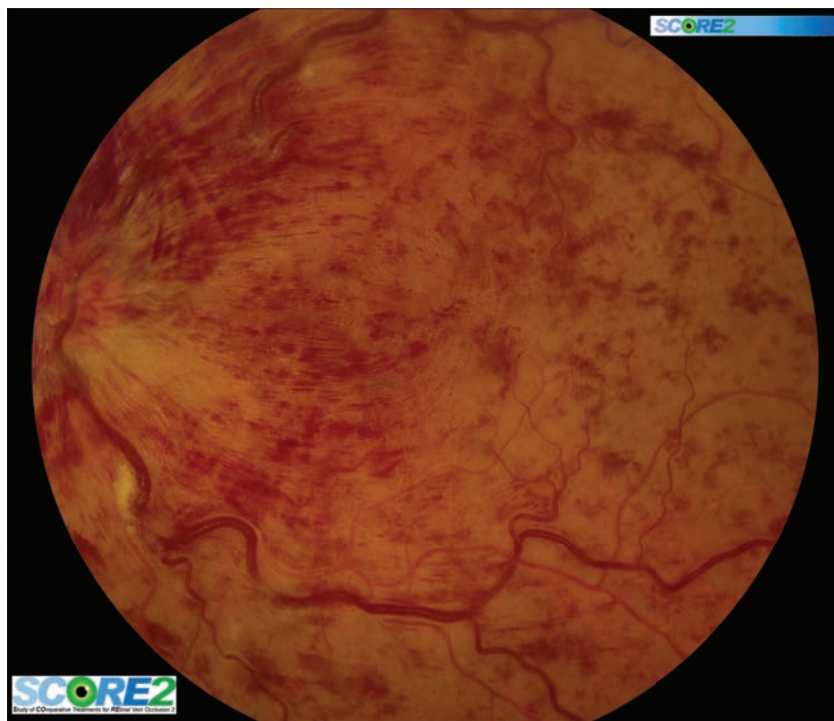


Figure. A baseline image from the *Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2)* trial showing central retinal vein occlusion associated with macular edema.

as central subfield thickness (CST) >300 μ m if measured with a Carl Zeiss Meditec Cirrus OCT machine or >320 μ m if measured with a Heidelberg Spectralis OCT machine.

Study eyes were randomized 1:1 to intravitreal bevacizumab (1.25 mg) every four weeks for six months vs. intravitreal aflibercept (2 mg) every four weeks for six months. Study visits were scheduled every four weeks for six months. The pre-specified primary outcome was change in best-corrected E-ETDRS VALS from baseline to month six, with the non-inferiority margin set at 5 letters.

The study enrolled 362 patients, of whom 180 were randomly assigned to aflibercept and 182 to bevacizumab. Participants' mean

age was 69 years, 43 percent were women, 76 percent white and 15 percent black. Mean VALS was 50 (approximate Snellen 20/100), and participants had macular edema for an average of seven months (range: zero to 104 months) before randomization. Mean CST was 666 μ m, 33 percent had received prior anti-VEGF treatment, 8 percent had prior intravitreal steroid treatment and 16 percent were diagnosed with HRVO.

Visual Acuity Gains

At month six, bevacizumab was non-inferior to aflibercept based on a VALS margin of five (bevacizumab minus aflibercept mean difference = -0.14; $p=0.001$ for non-inferiority). Mean VALS improved from 50.3 at baseline to

69.3 at month six in the aflibercept group, and improved from 50.4 at baseline to 69.3 at month six in the bevacizumab group.

In the aflibercept group, 65 percent of eyes had a ≥ 15 -letter gain in VALS at month six vs. 61 percent in the bevacizumab group. Fewer than 2 percent in each group had a ≥ 15 -letter loss in VALS at month six (aflibercept=3/175; bevacizumab=3/173). The proportion of patients who achieved a VALS of ≥ 70 (approximate Snellen of 20/40) in the study eye at month six was 58 percent in the aflibercept group and 57 percent in the bevacizumab group.

CST Reduction

Both groups demonstrated significant SD-OCT CST decreases from baseline through month six. With a baseline CST of 652 μm (SD=215 μm) in the aflibercept group, the mean decrease was 425 μm at month six. For the bevacizumab group, with a baseline CST of 678 μm (SD=233 μm), the mean decrease was 387 μm at month six.

The bevacizumab-minus-aflibercept estimate of the change from baseline treatment effect averaged over the six months was 49.3 μm in favor of aflibercept, a difference which is not statistically significant ($p=0.83$). In the aflibercept group, 54 percent of eyes had resolution of macular edema at month six compared with 29 percent in the bevacizumab group ($p<0.001$).

The Bottom Line

In sum, in SCORE2 participants with macular edema due to CRVO or HRVO, intravitreal bevacizumab was noninferior to intravitreal aflibercept with respect to visual acuity after six months of treat-

ment, based on a non-inferiority margin of a VALS of five. Both groups demonstrated significant decreases in CST from baseline to month six, with no significant difference between the groups with respect to the magnitude of CST reduction.

Of note, the proportion of eyes that achieved resolution of macular edema at month six was significantly lower in the bevacizumab group than in the aflibercept group. While this difference was not associated with a difference between study groups in visual acuity outcomes at month six, continued follow-up of SCORE2 participants will allow us to evaluate the cumulative effect of the presence of fluid on visual acuity and on the number of injections administered in participants assigned to the treatment groups not defined by a fixed-dosing schedule.

Ongoing follow-up will also provide information regarding longer-term outcomes, including visual acuity, need for continuing treatment, development of complications of CRVO and HRVO, quality of life and morphologic outcomes. ¹⁸

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QUALITY OF LIFE AND VITREORETINAL INTERVENTIONS

Payers want to know how much that medical intervention improves a patient's life. There's a way to measure that.

By **Melissa M. Brown, MD, MN, MBA**, and **Gary C. Brown, MD, MBA**

Quality of life in medicine is a nebulous term because it means different things to different people. Hundreds of different instruments to measure quality of life have been developed. Prof. Sam Salek discussed 120 quality-of-life instruments in a compendium published almost 20 years ago.¹ Hundreds more have been created since then. There is no criterion or gold standard quality-of-life instrument, explaining in part why so many quality-of-life instruments exist.

In retina, vitreoretinal interventions can improve a patient's quality of life (QOL) from less than a percentage point for genetic testing to 20 percent or more for anti-VEGF treatments for neovascular age-related macular degeneration. The table on page 32 lists QOL measurements for a variety of vitreoretinal procedures.

QOL measurements can help retina specialists when evaluating treatments for patients. But what does a 20-percent improvement in QOL mean, exactly? In this article, we'll explain what that means and look at existing tools for measuring quality after medical interventions, the limitations of those tools, and

how they apply to outcomes in vitreoretinal interventions.

Comparing Apples, Oranges

The major outcomes of clinical trials are typically specific to a specialty. Unless the primary outcome is death, they are very difficult to compare. For example, the Early Treatment Diabetic Retinopathy Study (ETDRS) utilized a three-line improvement in vision (20/80 to 20/40) as a major outcome.² The COMPASS Trial, which randomized patients with lower-extremity peripheral artery disease to aspirin, rivaroxaban (Xarelto, Janssen) or aspirin/rivaroxaban, used four major outcomes: number of hospi-

talizations; major adverse cardiovascular events; limb amputations; and death.³ Needless to say, it is impossible to compare the results of the ETDRS and COMPASS

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Trials utilizing the primary outcomes. So it is for thousands of clinical trials. (Incidentally, compared to aspirin alone, aspirin plus rivaroxaban decreased the incidence of major adverse limb events by 43 percent [$p=0.01$] and limb amputations by 58 percent [$p=0.01$].)³

Despite the increasing popularity of quantifying QOL, most clinical trials have not incorporated it into their primary outcomes. The result is that patient opinions regarding a specific disease state are often disregarded. Furthermore, while the specialty-specific, 25-question National Eye Institute Visual Function Questionnaire QOL instrument (NEI-VFQ 25) provides considerable information in comparing ophthalmic clinical trials, it is difficult to compare such specialty-specific QOL instrument outcomes across different specialties.⁴

As payers and health systems place more emphasis on patient-centered care,⁵ soliciting QOL estimates that are comparable across specialties seems reasonable.⁶

A conservative estimate holds that more than 27 million different input variables can comprise a cost-utility, or cost-effectiveness, analysis. Changing even one variable can prevent the comparability of two or more cost-utility analyses.⁷ In regard to QOL instruments and respondents, thousands of different input variables exist, and they are different enough that they can prevent comparability of the QOL results.⁶

Generic QOL Instruments

Two variants of QOL instruments exist: generic and specialty-specific.⁶

Generic instruments can theoretically be utilized to quantify the QOL associated with a health state

Take-home Point

As payers and health systems place more emphasis on quality outcomes and patient-centered care, they rely more on determining how medical interventions can quantitatively improve patient lives. In this climate, instruments for measuring quality-of-life gains are taking on new importance. This article explains the principles behind those instruments and explores the quality-of-life gains of specific vitreoretinal interventions.

(one or more diseases) or intervention across all specialties. Included among these instruments are:

- rating scales that ask patients to rate quality measures on a scale of zero to 100;
- the Short Form 36 and 12 surveys (SF-36, SF-12) that pose 36 and 12 questions, respectively;
- Quality of Well-Being (QWB) Scale;
- the Karnofsky Performance Status Scale; and
- different utility variants.⁶

Despite the hypothetical wide applicability of generic QOL instruments, they vary widely in terms of sensitivity to a health state, as well as reliability (reproducibility) and construct validity. Their utility to actually measure what they are intended to measure can be questionable.

We prefer utility analyses, in particular the time trade-off variant, for evaluations of ophthalmological health states. Utility analyses employ patient preferences. Patients can typically give up something of value (time of life, lesser risk of immediate death, money, etc.) to hypothetically improve their health state, or give up nothing and remain in the same health state.⁶ The main variants include time trade-off utility analysis, standard gamble utility analysis, willing-to-pay utility analysis and multi-attribute utility analysis.⁶

• **Time trade-off utility analysis.** We prefer the time trade-off

variant because it appears to have greater sensitivity, reliability and construct validity for ophthalmic health states than other variants.⁸⁻¹⁰ The anchors for utility analysis are usually 0.00 (death) and 1.00 (perfect health).

Visual time trade-off utilities have been shown to be typically unaffected by gender, age, ethnicity, level of education, wealth, comorbidities¹¹ and country of origin (in developed countries).⁷ They correlate most closely with vision in the better-seeing eye and decrease as the vision in the better eye decreases.¹² Utilities more closely correlate with the degree of vision loss rather than the underlying cause of vision loss.¹³

• **Bias.** Some authors have advocated the use of utility analysis in a manner that biases against the elderly and the disabled.¹⁴ The overall, mean systemic utility associated with each group is less than normal because of their associated disease profile. Let us assume the overall systemic utility is 0.80 in the average 85-year-old man.

Accordingly, if an ophthalmic or other intervention improves a patient's quality of life to 0.95, the patient will only be assigned an 0.80 utility because that is his overall systemic utility. A younger person or otherwise healthy individual will be assigned the 0.95. In essence, the elderly and disabled accrue less benefit from an intervention than the average person who is younger and has an overall utility of 1.00. We strongly disagree with this form of discrimination and do

Table. Quality of Life Associated with Vitreoretinal Interventions

Intervention	Quality-of-Life Gain (%)	Model*
Genetic screening for risk of neovascular age-related macular degeneration risk (becomes cost-effective if it allows an incremental 4.1% of nAMD patients age >65 years to be identified) ²³	0.71% 0.33%	S C
Laser photocoagulation for macular edema from branch retinal vein occlusion ²⁴	1.1%	C
Adventitial sheathotomy for macular edema from branch retinal vein occlusion ²⁴	1.8%	C
Proliferative vitreoretinopathy with retinal detachment repair by pars plana vitrectomy with perfluoropropane gas (C ₃ F ₈), no previous PPV ²⁵	1.9%	C
PVR with RD repair by PPV with C ₃ F ₈ , had previous PPV ²⁵	2.1%	C
PVR with RD repair by PPV with silicone oil, had previous PPV ²⁵	2.1%	C
PVR with RD repair by PPV with silicone oil, no previous PPV ²⁵	2.8%	C
Oral zeaxanthin added to triple therapy for neovascular AMD ²⁶	2.8%	C
Cryotherapy for threshold retinopathy of prematurity ²⁷	4.4%	C
Laser photocoagulation for subfoveal neovascular AMD ²⁸	4.4%	S
Oral supplements (AREDS 1) for Grade 4 Age-Related Eye Disease Study class (disciform scar in one eye and soft drusen in fellow eye) ²⁹	4.8%	C
Pegaptanib therapy, intravitreal, for subfoveal nAMD ³⁰	5.9%	S
Photodynamic therapy (PDT) with verteporfin for subfoveal neovascular AMD ³⁰	8.1%	S
Laser photocoagulation for choroidal neovascularization associated with histoplasmosis ³¹	8.1%	S
Laser photocoagulation for extrafoveal choroidal neovascularization ³²	8.1%	S
Corticosteroid therapy for immediate, vs. treatment at one week, for visual loss from giant cell arteritis ³³	11%	S
PDT with verteporfin for nAMD ³⁴	11.3%	S
Triple therapy (intravitreal bevacizumab + dexamethasone) + half-fluence PDT with verteporfin for neovascular AMD ²⁶	11.6%	C
Intravitreal ranibizumab for diabetic macular edema, assuming bilateral similar vision loss ³⁵	6.7% 4.9% 11.6%	F S C
Implantable miniature telescope insertion for severe AMD ³⁶	12.5%	C
Vitrectomy for idiopathic epiretinal membrane with macular pucker ³⁷	3.7% 12.9%	F S
Treatment of threshold ROP with laser photocoagulation ³⁸	13.1%	C
Oral zeaxanthin in combination with triple therapy for nAMD ²⁶	14.7%	C
Intravitreal ranibizumab for nAMD (2008 MARINA Trial) ³⁹	6.4% 15.8% 10.4%	F S C
Strontium plaque brachytherapy/intravitreal vascular endothelial growth factor inhibitor for nAMD ⁴⁰	12.3% 22.4% 15.8%	F S C
Intravitreal ranibizumab for nAMD (2017, updated MARINA & control data) ²⁰	9.8% 22.8% 16.3%	F S C
PPV for diabetic vitreous hemorrhage ⁴¹	24.2%	C
Early ranibizumab treatment for nAMD (baseline vision of 20/40 to 20/80) ²³	13.1% 32.3% 21.3%	F S C
Late ranibizumab treatment (baseline vision of 20/160 or less) of nAMD ²³	3.8% 9.5% 6.3%	F S C
Early ranibizumab treatment of nAMD (vision 20/40 to 20/80), versus later treatment (vision <29/160) quality of life gain ²³	8.4% 20.8% 13.7%	F S C

*KEY: S = second-eye model; F = first-eye model; C = combined-eye model

not believe the public in the United States will accept it.

• **Utility respondents.** The respondent cohort—community, experts, physicians, researchers, administrators, surrogates—is as important as standardization of the instrument used to assess QOL. As an example, ophthalmologists, when asked to estimate the QOL associated with different levels of severity of AMD, underestimated the adverse effect of the disease by 96 to 750 percent compared to the actual patients with AMD.¹⁵ Medical students, non-ophthalmologists and the general community were even worse in estimating the adverse effects of vision loss upon patient QOL.^{16,17}

All of the QOL values in this article were derived from ophthalmic patients using time trade-off utility analysis. Thus, all are comparable, unlike those from papers utilizing different QOL instruments and varied respondents.

• **One eye or two?** Ophthalmic interventions are unique in that we have two eyes. Research has shown that the treatment of one eye, when the fellow eye still has good vision (first-eye model) confers less QOL gain than treatment of the second eye when vision in the first eye has already been lost to a disease (second-eye model).¹⁸ A combined-eye model, in which integrated first-eye and second-eye models are weighted, is preferable and most closely simulates the actual clinical condition. The table lists the types of vision utility models utilized.

Specialty-specific Instruments

More numerous than the generic instruments, hundreds of specialty-specific instruments exist. They include the NEI-VFQ 25 question-

naire), the Modified Rankin Scale for stroke, the American College of Rheumatology Classification of Global Functional Status in Rheumatoid Arthritis and the GOLD

Quotable

Ophthalmologists, when asked to estimate the quality of life associated with different severity levels of age-related macular degeneration, underestimated the adverse effect of the disease by 96 to 750 percent.

Classification (Global Initiative for Chronic Obstructive Lung Disease).⁶ These instruments can provide good comparability information within specialties or subspecialties, but typically have limited applicability for health states and interventions across specialties due to different sensitivities, reliability difficulties and questionable construct validity.⁶

Why QOL of Vitreoretinal Interventions Is Different

Many authors describe patient value gain (improvement in quality of life and/or length of life) in terms of QALY (quality-adjusted life-year) gain; most do not elect to calculate the percent QOL gain as we do in our Value-Based Medicine analyses. Because ophthalmic interventions do not usually affect length of life,

patient value gain is most often the same as QOL gain and can be readily calculated as a percentage.

The QOL gains shown are all associated with the Center for Value-Based Medicine; thus, all are comparable. A number of factors can prevent comparability among QOL analyses. They include different utilities, unlike utility respondents, lack of a 3-percent annual discount rate as recommended by the Panel on Cost-Effectiveness in Health and Medicine,¹⁹ utility calculations variations, and lack of sufficient data in the manuscript. The QOL gains listed in the table were all calculated as part of a cost-utility analysis. The cost-utility ratios are not listed and are outside the scope of this article.

A note about the 3-percent discount rate: This applies to both QOL (patient value gain) and dollar value, which is discounted due to the time value of money (money in the future is worth less than money today); and the fact that good health now is worth more than it is in the future because good health now can enable a person to earn money that can be invested.

An additional note on the ophthalmic models, though not the systemic models, is warranted. Typically, first-eye models (F) yield the lowest QOL gain because the fellow eye is presumed to be normal. If the fellow eye has 20/20 vision and the vision in the treated eye improves from 20/100 to 20/60, most patients do not notice an appreciable difference in their overall QOL. However, when vision in the second eye deteriorates, and the first eye already has vision loss, there is typically a much larger QOL gain from the same intervention vs. when it was performed in the first-eye model.⁶

Combined-eye Model

The combined-eye model weights to the first-eye and second-eye models to provide the best simulation of the clinical scenario. The first-eye model alone tends to underestimate QOL gain, while the second-eye model tends to overestimate it.⁶ For example, in a follow-up MARINA trial cost-utility analysis in 2017 assessing ranibizumab (Lucentis, Roche/Genentech) for the treatment of nAMD,²⁰ the first-eye model QOL gain of 16.3 percent underestimated the combined-eye model by 41 percent. The second-eye model overestimated the QOL gain by 40 percent.

Of special note is the dramatic gain in QOL in nAMD with ranibizumab for early treatment (baseline vision 20/40 to 20/80) vs. late treatment (vision < 20/160) (*Table*). Taking both eyes into account, early treatment results in a 21.3 percent QOL gain vs. a 6.3 percent QOL gain for late treatment.

Overall, there is a great range of QOL gains associated with vitreo-retinal interventions, most of which compare favorably with nonvitreo-retinal ophthalmic and systemic interventions. We did not address the associated costs of the interventions listed, but many have a considerable financial return-on-investment to society for the direct medical costs expended.

Economist William Nordhaus, PhD, reported that health-care advances accounted for 50 percent of the wealth accrued in the United States in the 20th century.²² We should be pleased that our interventions provide not only improvements in QOL, but also make the United States a wealthier country by giving patients greater independence and the ability to work. 

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RETINA STANDOUTS FROM ARVO 2018

NOVEL TREATMENTS FOR RP, CSC AND MORE

*Promising results of topical treatment for macular holes,
non-drug anesthesia for IVT and RRD repair without prone positioning.*

By Ashkan M. Abbey, MD

The field of retina continues to evolve and advance rapidly through the work of outstanding researchers from the laboratory bench to the bedside. The annual meeting of the Association for Research in Vision and Ophthalmology—ARVO2018—in Honolulu showcased the latest in diagnostics, treatment and management strategies for retinal disease, while also providing a glimpse into the future of retina with intriguing translational research.

Here, we report on five compelling posters and presentations. They include a novel gene editing technique and delivery modality for a form of autosomal dominant retinitis pigmentosa, oral mifepristone for treatment of central serous chorioretinopathy, topical dorzolamide-timolol for macular holes, vitrectomy without prone positioning for retinal detachment repair, and a novel device for rapid non-pharmacologic anesthesia prior to intravitreal injections.

CRISPR-Cas9 Gene Therapy For Retinitis Pigmentosa

Currently, the only approved treatment for retinitis pigmentosa is a retinal prosthesis for patients with profound vision loss. *RHO* is the most common gene involved in autosomal dominant RP (ADRP). CRISPR-Cas9—CRISPR stands for clustered regularly interspaced short palindromic repeats, and Cas9 for CRISPR-associated system⁹—is a gene-editing technique that relies on a guide RNA that can be programmed to target different

genomic loci.

In this study, the researchers successfully utilized CRISPR-Cas9 to target and edit out the human *RHO* gene responsible for this form of ADRP in human embryonic kidney (HEK293) cells.¹ Importantly, the researchers were able to effectively deliver the CRISPR-Cas9 ribonucleoprotein complex using a lipid nanoparticle. They then used polymerase chain reaction to confirm that the *RHO* gene was successfully silenced.

ABOUT THE AUTHOR



Dr. Abbey is a surgical and medical retina specialist at Texas Retina Associates, Dallas, and clinical assistant professor of ophthalmology at the University of Texas Southwestern Medical Center.

DISCLOSURE: Dr. Abbey is a consultant for Allergan and Genentech.

Take-home Point

Five presentations from the Association for Research in Vision and Ophthalmology 2018 meeting in Honolulu get a second look: a gene editing technique utilizing the CRISPR platform to treat autosomal dominant retinitis pigmentosa; short-term use of a glucocorticoid receptor antagonist to reduce subretinal fluid in central serous chorioretinopathy; use of a topical dorzolamide-timolol combination to close macular holes; a study of not using prone positioning in patients who had vitrectomy for rhegmatogenous retinal detachment; and use of a non-pharmacologic, cooling-based technique to anesthetize the ocular surface before intravitreal injections.

This is the first study to demonstrate the effective use of nanoparticles (instead of viral vectors) transfected with CRISPR-Cas9 for gene editing of a retinal disease. This gene editing technique allows for disruption of both normal and mutated alleles of the *RHO* gene, which is critical for effective treatment of ADRP. The results provide a promising step forward in finding a potential treatment for a common form of RP.

Mifepristone for Central Serous Chorioretinopathy

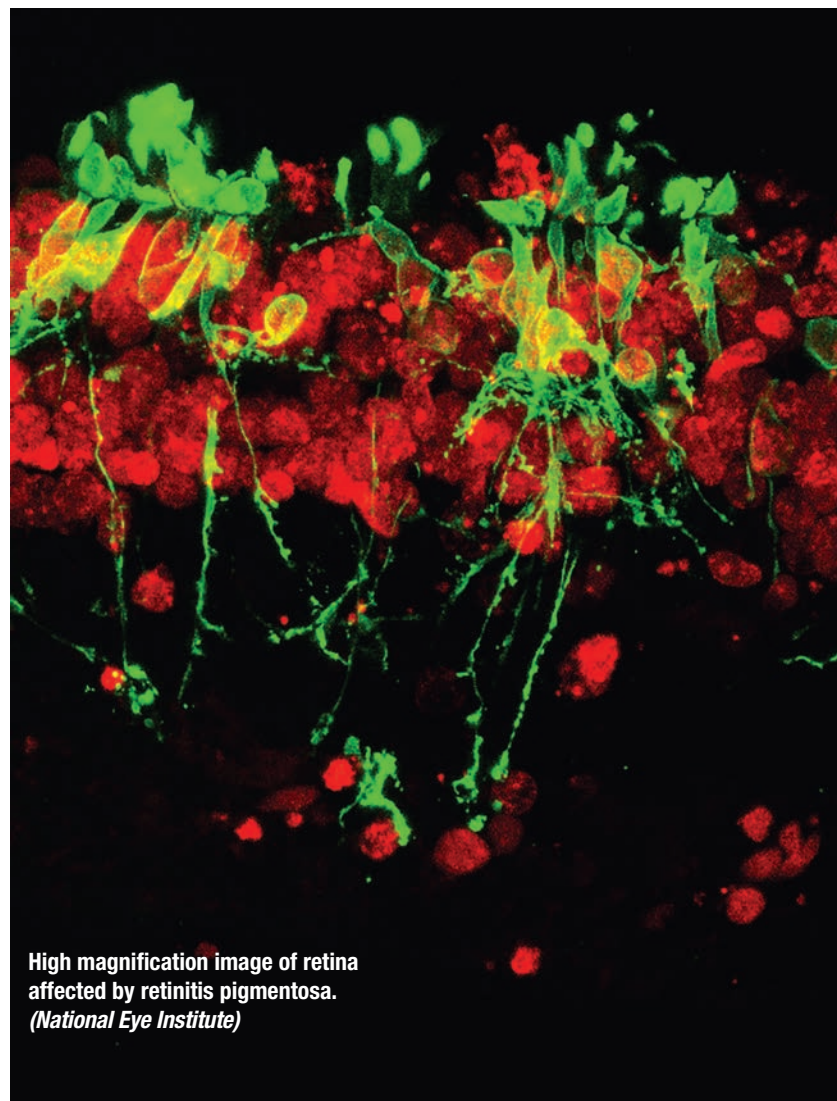
The short-term use of oral mifepristone, a glucocorticoid receptor (GR-2) antagonist with high oral bioavailability, may reduce subretinal fluid and improve vision in patients with central serous chorioretinopathy (CSC). CSC is associated with elevated serum cortisol levels. Mifepristone antagonizes cortisol action competitively at the glucocorticoid receptor level.

In this randomized, double-masked, multi-site, placebo-controlled trial, 30 patients with chronic and/or recurrent CSC were randomized into three groups:²

- mifepristone 300-mg daily for four weeks;
- mifepristone 900-mg daily for four weeks; and
- placebo for four weeks.

After dosing, all patients were followed for four weeks for observation. After eight weeks, the researchers noted a statistically significant reduction of central retinal thickness (CRT) of 82 μm ($p<0.05$) and improvement in best-corrected visual acuity of 3.6 letters ($p<0.05$) in the treatment groups.

Patients that received placebo did not have a significant change in CRT (47 μm , $p=0.45$) or BCVA (0.7



letters, $p=0.64$). However, neither the change in CRT ($p=0.15$) nor change in BCVA ($p=0.19$) achieved a statistically significant difference between the two treatment groups.

The authors reported that mifepristone was well tolerated in the trial. Larger studies are warranted to further investigate the safety and efficacy of this medication in CSC, but mifepristone appears to be a promising new agent that can be added to our armamentarium for the treatment of chronic and/or

recurrent CSC.

Topical Dorzolamide-Timolol For Macular Holes

Hydration of retinal tissue may play a significant role in macular hole formation. Topical dorzolamide-timolol may assist in the closure of some macular holes through cystoid dehydration. In this study, a series of four patients with idiopathic full-thickness macular holes received twice-daily topical dorzolamide-timolol. All included holes

were less than 300 μm in diameter.³

Two of the four holes closed spontaneously after four weeks of topical dorzolamide-timolol and had associated improvement in vision. Both eyes remained stable, and the holes remained closed after six months of follow-up. Larger, controlled studies will be useful to validate the possible role of cystoid dehydration with topical dorzolamide-timolol in the closure of full-thickness macular holes.

Vitrectomy Without Prone Positioning for RRD

Prone positioning after pars plana vitrectomy (PPV) is often quite challenging for the recovering postoperative patient. Previous studies have demonstrated that PPV for macular holes without postoperative prone positioning had excellent closure rates. In this study, the authors demonstrated that PPV without prone positioning was associated with a higher reattachment rate in eyes with a rhegmatogenous retinal detachment (RRD), particularly those with inferior retinal breaks.⁴

This retrospective cohort study included 142 eyes with a primary RRD. All patients underwent PPV with 20% sulfur hexafluoride gas tamponade. All phakic patients received simultaneous cataract surgery. The patients were then divided into two groups: Those who were advised to maintain prone positioning, and those who were not. The patients who were advised not to maintain prone positioning were instructed to sleep in a supine position. All patients were followed for more than three months.

Of the 142 eyes, 65 underwent postoperative prone positioning and 77 went without prone positioning. The initial reattachment rate was

96.1 percent in the group without prone positioning vs, 83.1 percent in the prone-positioning group. The authors noted this difference was statistically significant ($p=0.011$).

In RRDs without inferior breaks, the initial reattachment rate was similar in both positioning groups. In RRDs with inferior breaks, the initial reattachment rate was significantly higher without prone positioning (94.7 percent vs. 60 percent with prone positioning, $p=0.036$). Despite the higher overall reattachment rate, patients that did not perform prone positioning had a higher incidence of epiretinal membrane (ERM), although it did not achieve statistical significance (17.8 percent vs. 4.9 percent, $p=0.092$).

This study demonstrates that maintaining a strict prone position may not be a requirement after PPV for RRD in pseudophakic eyes. The data may convince more surgeons to liberate their patients from the burdensome requirement of postoperative prone positioning, even in those with inferior breaks. However, the increased possibility of ERM in these patients may influence the surgeon's positioning recommendations.

Non-pharmacologic Anesthesia for IVT

A novel non-pharmacologic, cooling-based method for providing ultra-rapid anesthesia before intravitreal injection (IVT) was well tolerated when compared to lidocaine-based anesthesia. The portable, handheld device utilizes thermoelectric cooling to rapidly anesthetize a 4-mm-by-4-mm area on the surface of the eye before the injection.

This randomized, prospective, unmasked clinical trial included 20

patients who were receiving bilateral IVT for either neovascular age-related macular degeneration or diabetic macular edema.⁵ One eye was randomized to lidocaine-based anesthesia (3.5% lidocaine gel), while the fellow eye received ultra-rapid, non-pharmacologic anesthesia.

Subjective pain was assessed at the time of IVT and four hours afterward, and responses were recorded via visual analog scale (from 1 to 10). Subjective pain scores at the time of injection were 2.9 ± 0.47 for subjects receiving topical lidocaine, and 2.7 ± 0.41 in the treatment group ($p=0.7$, mean $\pm$ standard error of mean [SEM]). Postinjection pain scores were 1.7 ± 0.5 for topical lidocaine and 1.5 ± 0.43 in the treatment arm ($p=0.7$, mean $\pm$ SEM).

Ultra-rapid cooling for non-pharmacologic anesthesia demonstrated similar patient-reported pain scores when compared to anesthesia with topical lidocaine gel. This anesthesia device may someday offer a more efficient and tolerable injection procedure for both patients and physicians. 

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CLINICAL CONVERSATION

CORTICOSTEROIDS FOR DME: LESSONS FROM PROTOCOL U

Our expert panel parses how the DRCRnet trial informs how they use of corticosteroids in diabetic macular edema. Part 2 of 2.

Reported by Richard Mark Kirkner, Editor

In the second part of this Clinical Conversation, Protocol U of the Diabetic Retinopathy Clinical Research Network study^{1,2} provides a backdrop as *Retina Specialist* Chief Medical Editor Charles C. Wykoff, MD, PhD, leads our expert panel through a discussion of their approaches for using corticosteroids to manage diabetic macular edema. The panelists discuss how Protocol U has influenced their approach to DME, including how they add the corticosteroid and timing. They also discuss how they manage intraocular pressure response to corticosteroid treatment.

Protocol U was a Phase II trial that evaluated the effectiveness of the dexamethasone intravitreal implant (Ozurdex, Allergan) in combination with anti-VEGF therapy for treatment of persistent DME.^{1,2}

How Do You Use Corticosteroids in DME?

Dr. Wykoff asks the panelists if Protocol U has changed how they

incorporate corticosteroids into their management of DME? The panelists concur that anti-VEGF treatment remains their first-line therapy for DME, but that cortico-

steroids have a place as second-line treatment

Judy E. Kim, MD, continues to use corticosteroids as a second-line therapy after a series of anti-VEGF

Take-home Point

In the second of two parts exploring Protocol U of the Diabetic Retinopathy Clinical Research Network, this expert panel discusses how they use corticosteroid therapy to manage diabetic macular edema, mostly as a second-line therapy for patients who don't respond to anti-VEGF drugs. They also talk about their timing for starting corticosteroid therapy, and how they manage spikes in intraocular pressure.

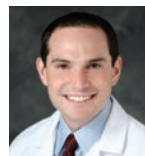
Clinical Conversation Expert Panel



Judy E. Kim, MD, is a professor of ophthalmology, specializing in vitreoretinal diseases and surgery, at the Medical College of Wisconsin in Milwaukee.



Michael Singer, MD, is a clinical professor of ophthalmology at the University of Texas at San Antonio, and director of clinical research at Medical Center Ophthalmology Associates in San Antonio.



Michael Ober, MD, is a partner at Retina Consultants of Michigan in Southfield, and associate professor of ophthalmology at Oakland University, William Beaumont School of Medicine, Royal Oak, Mich. He is also an adjunct teaching professor at Henry Ford Health System, Detroit, and chief of staff at Straith Hospital for Special Surgery in Southfield, Mich.



Moderator: Charles C. Wykoff, MD, PhD. Dr. Wykoff is chief medical editor of *Retina Specialist*, director of research at Retina Consultants of Houston and deputy chair of ophthalmology at Blanton Eye Institute, Houston Methodist Hospital.

injections in patients with persistent DME with intraretinal fluid or subretinal fluid. “Other patients for whom I consider using steroids rather than anti-VEGF agents include patients who are pregnant or nursing, have had a recent stroke, or those who are pseudophakic and have no history of steroid-induced glaucoma but cannot come in on a frequent basis for anti-VEGF treatments,” she says.

Likewise, Michael Ober, MD, says anti-VEGF remains his first line therapy due to its safety profile. “I see Protocol U as a validation of my current regimen,” he says.

However, there is one exception in his approach: “If after several regular anti-VEGF treatments I don’t see the improvement I expect, I will give a steroid injection and then see the patient again one month later rather than combine the two treatments at once,” he says. “If in a month cystic changes and/or subretinal fluid have not improved significantly, I’ll supplement it with anti-VEGF monthly as needed.”

Michael Singer, MD, notes that he adds a corticosteroid when patients become sub-responders or non-responders either because of an anatomic issue, or because they can’t keep up their visits for anti-VEGF treatments or they get injection fatigue.

“I know, based on the work we’ve done in retinal vein occlusion that we’re able to get three to four months’ worth of treatment with a steroid,” Dr. Singer says. “Having that opportunity in the long term may increase compliance if they don’t have to come in as often.” He’ll also consider steroids to extend the treatment interval as the patient completes the first year of anti-VEGF therapy.

Centrifuge-concentrated Intravitreal Triamcinolone

The go-to corticosteroid treatment for Michael Ober, MD, is centrifuge-concentrated intravitreal triamcinolone.³ When he gives the steroid, he times patient visits at intervals just prior to the expected absorption of the steroid. “I’ll give them combination therapy only if there’s persistent edema,” he says. “Most of the time, they don’t need the combination therapy.”

At this point, Dr. Ober will incorporate as-needed supplemental treatments. When giving patients either dexamethasone or triamcinolone, he’ll have them return in a month. If the edema is persistent at that point, he will supplement with anti-VEGF treatment. “But if the edema is not persistent, it is one of the few times I will use a p.r.n. protocol,” he says. “I’ll usually have the patient come back when I think the steroids are going to wear off.”

He adds that 0.03 ml of centrifuge-concentrated intravitreal triamcinolone typically lasts three months while 0.05 ml lasts five months. He rarely gives larger volumes even though he reported 0.1 ml lasts eight months on average.³

Logistics of Adding the Steroid

Dr. Singer uses a combination treatment like that employed in Protocol U. “I won’t do it on the same day for insurance reasons,” he says. He waits two weeks to see if the anti-VEGF injection has had an effect. “At two weeks some of these patients have persistent edema, and that lets me know if the anti-VEGF completely dried out the retina or at least started to,” he says.

The degree of retinal dryness is a marker of the cause of the edema, Dr. Singer says. “If the retina is only 20 percent dry after an anti-VEGF injection as opposed to 80 percent dry, that indicates it is more inflammatory-mediated,” he says. “If it’s more than 50 percent dry, it is anti-VEGF mediated, but the anti-VEGF agent is not strong enough. In these cases I’ll switch to a stronger anti-VEGF agent.”

Because DME has a vascular endothelial growth factor component, anti-VEGF therapy always has a role in these patients, he says. “Treatment with anti-VEGF is going to handle the VEGF portion, even if it’s minor, and the steroid will handle the inflammatory component,” he adds.

Dr. Kim says she may switch from

anti-VEGF to a monotherapy steroid. In some cases she favors combination therapy. “In some patients I will use the dexamethasone implant one month, then anti-VEGF for the second and third months, followed by dexamethasone again the following month,” she says. “However, I’m not doing combination therapy on the same day or within a week.” The dexamethasone implant lasts three months on average, but it can range from two to five months, she says.

Managing Side Effects

Dr. Wyckoff notes that 29 percent of the combination group in Protocol U had increased IOP but none of the ranibizumab monotherapy arm did. The study duration was probably too short to adequately assess cataract progression.

Dr. Singer points out that the REINFORCE trial of the dexamethasone intravitreal implant had low percentages of patients with IOPs over 25 and 35 mmHg—8.2 percent and 1 percent, respectively.⁴ Overall, 22 percent of patients needed IOP therapy. He uses either monotherapy or combination drops to treat IOP, “and the vast majority of patients handle that well.”

Dr. Singer notes that, as the

steroid wears off, the need for anti-glaucoma drop decreases. “Then when you give another steroid injection, you may have to keep them on the anti-glaucoma therapy,” he says.

Dr. Kim finds that about 20 percent of her patients on steroid therapy have increased IOPs, but, again, most respond to pressure-lowering drops. “Glaucoma surgery has only been needed in rare cases,” she adds.

Clinical Threshold for Drops

Key factors for starting a patient on IOP-lowering drops include the patient’s age, optic nerve appearance, history of glaucoma and baseline IOP, Dr. Ober says.

Those patients, he says, are “going to have a much lower threshold to begin IOP-lowering therapy than those without risk factors for glaucoma.” He frequently comanages these patients early with a glaucoma specialist if they need two or more drops. “The optic nerve evaluation or OCT nerve fiber layer interpretation can sometimes have more nuance to it,” he says.

When To Shift to Fluocinolone

Dr. Singer puts patients on fluocinolone when the treatment burden becomes an issue; that is, when injection fatigue sets in but the retina is very stable, and when he’s assured they are not going to have a significant IOP response after dexamethasone. “I monitor these patients carefully,” he says.

Some patients on fluocinolone may need supplemental therapy, but others may experience rebound edema. Dr. Singer notes he retreats those patients with rebound edema with an anti-VEGF injection. “In my experience, unlike with typical anti-VEGF injections that last only

a month or two, patients on the fluocinolone implant can extend out anti-VEGF treatment to three to four months,” he says. “My hypothesis is that because the anti-VEGF injection only has to deal with the VEGF component, while the micro-dosing of the steroid seems to handle the inflammatory component.”

Dr. Kim goes to fluocinolone after the patient shows a good response to dexamethasone but must continue with treatment. “At that point, I switch to fluocinolone in order to reduce the treatment burden,” she says.

Dr. Ober opts instead for the centrifuge-concentrated triamcinolone in these situations (*box, page 39*). “That sort of works in lieu of the fluocinolone, and it’s much less expensive,” he says. This is the so-called slurry steroid that he originally reported in 2013. He uses Triesence. Susan Malinowski, MD, reported on the same technique using Kenalog.⁵ Says Dr. Ober, “I can give a dose as low as 0.01 ml. My standard dose is 0.03 ml; that will last usually three to four months.” ^{RS}

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(Continued from page 12)

fluid resolved after IOP-lowering surgery.^{2,4} On the other hand, macular schisis has been reported in patients with normal-tension glaucoma, which argues against the role of elevated IOP.⁷

Management of this entity can vary. As seen in our case and others,^{2,4} surgery to address uncontrolled glaucoma can lead to resolution of fluid. Spontaneous resolution has also been reported, which makes observation a reasonable option.⁶ Pars plana vitrectomy with gas tamponade has also been employed successfully.² ^{RS}

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A Smaller, Faster Anti-VEGF Therapy

How brolucizumab may extend dosing out to 12 weeks.

By Richard Mark Kirkner

The quest for vascular endothelial growth factor antibodies that require less than monthly dosing has been ongoing since ranibizumab (Lucentis, Roche/Genentech) gained approval for treatment of wet age-related macular degeneration. The paradigm shifted in 2014 when aflibercept (Eylea, Regeneron) was approved for eight-week dosing for diabetic macular edema, and while treat-and-extend protocols have made significant progress in stretching the intervals between injections, patients and retina specialists have to go through months of trial and error before they arrive at a routine.

The paradigm may shift again. Results from the HAWK and HARRIER trials reported at the Association for Research in Vision and Ophthalmology have shown that retina specialists may be able to ramp up quickly to 12-week intervals with Novartis' anti-VEGF candidate brolucizumab.

Pravin Dugel, MD, of Retinal Consultants of Arizona, first reported the HAWK and HARRIER results at the American Academy of Ophthalmology Retina Subspecialty Day Meeting in 2017. He reported that 57 percent and 53 percent of patients in the trials, respectively, could be extended to every 12-week dosing after a loading dose.¹ He additionally reported that in a head-to-head comparison vs. aflibercept (Eylea, Regeneron) at week 16, brolucizumab showed superior results on optical coherence tomography.

Brolucizumab, also known as RTH258, is a single-chain antibody fragment (scFv). Its small molecular size of 26 kilodaltons (kDa) enables

the agent to penetrate tissue more effectively and clear more rapidly from systemic circulation than large-molecule drugs.⁴⁻⁶ By comparison, the average protein has a molecular weight of 34 kDa, while ranibizumab's (Lucentis, Roche/Genentech) is 48 kDa and aflibercept's 115 kDa.

At ARVO, Glenn J. Jaffe, MD, of Duke University reported on important anatomical markers from HAWK and HARRIER that demonstrated brolucizumab was non-inferior to aflibercept for mean change in best-corrected visual acuity, but superior in terms of reductions in central subfield thickness and incidence of intraretinal and subretinal fluid after 48 weeks.²

Dr Dugel also reported predictability rates of 82 percent and 87 percent in HAWK and HARRIER in patients who successfully completed the initial 12-week cycle remaining on this cycle up to week 48.³

In its annual report, Novartis noted that this year it would file new drug applications in the United States, Europe and Japan for brolucizumab for treatment of nAMD and begin Phase III trials for diabetic macular edema, with filing expected for that indication in 2020. Analysts say they expect the Food and Drug Administration to approve brolucizumab for nAMD next year.

Here, Dr. Dugel, a principal investigator of HAWK and HARRIER, answers questions about brolucizumab.

Q The mechanism of action in his own words.

A Brolucizumab is unique in that it's the first single-chain antibody fragment in ophthalmology. The target is the same as other anti-VEGF

antibodies: VEGF-A. What's different is the structure of the drug. An antibody is shaped like a Y, but only the tips of the Y carry the active component that interacts with the target; the rest of the structure provides stability. Brolucizumab is different because it is essentially only the tips of the Y. This gives the drug a smaller size and a higher molar concentration than existing anti-VEGF treatments.

Q How does brolucizumab differ from existing anti-VEGF agents?

A The molar concentration of brolucizumab is 11 to 13 times higher than aflibercept. The smaller molecule size and high molar concentration means that the time of action may be earlier and the durability may be longer. An analogy is soccer, where you have 11 players on either side with the same size goal. The pharmacokinetics of brolucizumab are like having 144 players on the other side. The dimensions of the goal haven't changed, but the probability of achieving that goal has.

Q What unmet need does brolucizumab meet?

A Wet AMD and diabetic macular edema are extraordinarily variable diseases. Some patients need to be treated intensely, others less so. We need a drug that can address individualized treatment needs. That is, how can we have a drug that has a higher molar concentration, that acts earlier and lasts longer in both types of patients? HAWK and HARRIER were designed to address treatments in both types of patients. In that

(Continued on page 45)



Yet Another Medicare Audit Process

Here's what you can expect from and how you can prepare for a Targeted Probe and Education review.

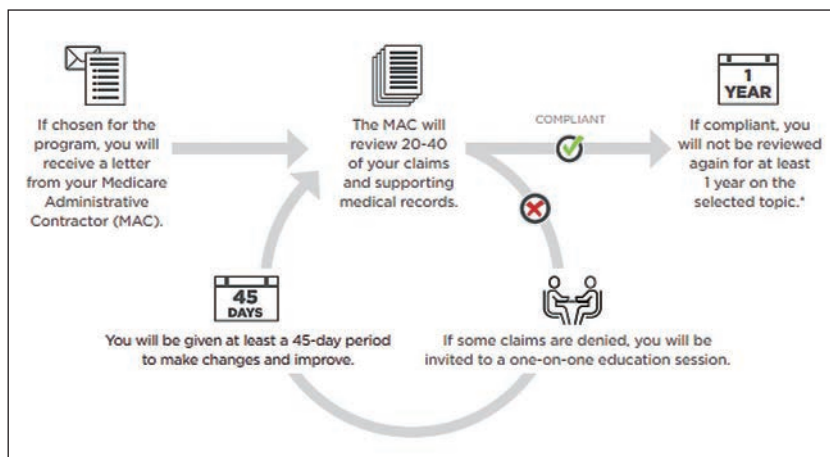
Yes, the headline is correct. The Centers for Medicare and Medicaid Services (CMS) developed another process to audit and monitor provider claims. In 2014, CMS initiated a pilot program called Targeted Probe and Education, or TPE. Due to its success and “favorable outcomes,” TPE is being rolled out to all Medicare Administrative Contractors (MACs). On September 15, 2017, Change Request 10249 expanded the TPE program to include all MACs effective October 1 last year.¹ According to CMS, “The process is only used with those who have high denial rates or unusual billing practices.”²

Targeted Topics

During the pilot program, CMS chose the topics for review. Now, the MACs will be choosing the topics under review. As of this writing, only one MAC, Novitas Solutions Inc., which covers 11 states and the District of Columbia, has published a list of topics for review.³ The list includes some services like new and established Evaluation and Management (E/M) office visit codes (99201 to 99205 and 99211 to 99215). More specific to the subspecialty of retina, two high-volume drugs are on the list:

- J0178 – Injection, aflibercept, 1 mg; and
- J2778 – Injection, ranibizumab, 0.1 mg.

Novitas—not to be confused with Novartis—provides key points regarding injections and billing for drugs.⁴ The following topics are listed for injection services:



How the Targeted Probe and Education review process works. A provider gets three rounds to be compliant to avoid further action. (Image provided by Centers for Medicare and Medicaid Services.)

- Where the sole purpose of an office visit was for patient to receive an injection, payment may be made only for the injection service (if it is covered).
- Pay separately for those injection services only if no other physician fee schedule service is being paid.
- The drug is separately payable.
- All injection claims must include specific name of the drug and dosage.

Novitas further conditions that drugs and biologicals are covered if all requirements are met:

- Not usually self-administered by patients.
- Meet all general requirements for coverage of items as incident to a physician's services.
- Reasonable and necessary for diagnosis or treatment of illness or injury for which they are administered according

to accepted standards of medical practice.

- Not excluded as immunizations.
- Have not been determined by Food and Drug Administration (FDA) to be less than effective.

Novitas lists the TPE “start date” for new patient E/M codes to begin June 2018, established E/M codes to begin in August, and the TPE process for drug injections to begin in May and June.

The TPE Process

A targeted review of providers with high denial rates or unusual billing practices determines who will be audited. As subspecialists, retinal specialists, when compared to all of ophthalmology, are outliers. Being an outlier does not mean you are doing something wrong; it only means subspecialists have different claims and billing patterns.

If the TPE process targets a clini-

If You Receive a Request for a TPE Review

When responding to a request for a Targeted Probe and Education review, the goal is to submit supporting documentation and receive a compliant rating so the process ends. We encourage you to do the following prior to submission:

- Respond promptly within the designated time.
- Review operative reports for injections of ranibizumab (Lucentis, Roche/Genentech) or aflibercept (Eylea, Regeneron).
- Look for documentation supporting the volume and units of drug injected.
- Confirm that units align with indications.
- Look for identifying information such as “lot” and “inventory” numbers to reconcile.
- Verify that samples were not billed.
- Prepare an abbreviation list to “decode” notes if necessary.
- Attach a signature log when handwritten signatures are used or not identified.
- For Evaluation and Management (E/M) codes, do not overlook relevant history questionnaires completed by the patient.
- Dictation or correspondence may help support E/M levels of service.

cian, the MAC will send a letter to the provider asking for supporting documentation for 20 to 40 claims. After submission, the auditor for the MAC will review the supporting documentation and the MAC will notify the clinician of the outcome of the review.

If the claims are compliant, the process likely ends for the targeted topic for at least one year. However, if claims are denied or the audit identifies issues, the clinician gets a “one-on-one” education session. Following the education session, the provider is given 45 days to make changes and improve. After the 45 days the process starts over and the MAC reviewer requests another sample of 20 to 40 claims, but for dates of service after the one-on-one session.⁵

If the practice is still non-compliant or unsuccessful after three rounds and fails to show adequate improvement, the provider will be referred to the CMS for the next steps. They may include 100 percent prepay review, extrapolation, referral to a recovery auditor or other action.⁶ All of this increased scru-

tiny can create significant problems for the practice.

Following each round, the provider receives a letter that details the results of the review. Unfortunately, the acceptable error rates are not published and may vary by MAC. The letter may arrive before or after the one-on-one education.⁷

Each provider has three rounds to show compliance to avoid further action beyond TPE. It is also possible that a clinician could be involved in more than one TPE at a time. For example, a request for E/M and ranibizumab (Lucentis, Roche/Genentech) claims could occur concurrently.

Monitor Your MAC for Updates

CMS says the TPE process will reduce the number of providers receiving audit requests. The agency’s goal is “to help you quickly improve.” During the pilot program, we received a few calls from clients submitting documentation. Each client submitted what was requested, and we have yet to hear of anyone subjected to more than one or two rounds in the pilot TPE process.

The TPE rollout is new and therefore it’s too early to know how each MAC will handle it. Watch for any TPE requests and do your best to submit thorough documentation supporting any claims in the request. For additional information, monitor your MAC for any MAC-specific updates. 

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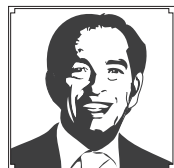


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CLINICAL TRIAL CLOSEUP

(Continued from page 41)

regard, what HAWK and HARRIER showed was that at week 16, which is a very important milestone, brolicizumab was superior to aflibercept in every anatomical parameter studied by optical coherence tomography.

Q What was new about the HAWK and HARRIER results reported at ARVO?

A HAWK and HARRIER had several prespecified time points of disease activity assessment; if patients had active disease, they were adjusted to q8-week dosing. The results presented at ARVO looked at the likelihood that those who completed the first q12-week dosing cycle would remain on q12-week dosing through the primary endpoint at year one.

The high percentage of patients that were able to continue on q12-week dosing in the latest HAWK and HARRIER results is consistent with the Phase I and Phase II OSPREY trials.^{1,7} That's quite impressive in my opinion. This says that if you use the clinically defined criteria, and you are able to extend somebody to a q12-week cycle at initial treatment, the chance that that person is going to stay on that q12-week cycle is almost 90 percent. That should give the clinician greater confidence, in terms of predictability, to extend patients.

Q What are the next steps in the HAWK and HARRIER trials?

A There is still a great amount of data from these trials that needs to be analyzed. Those results will be reported at upcoming meetings. There's also an extension study, per the FDA, that's a perfunctory study to ensure that the drug's manufacturing is consistent. The filing will follow that. As with other anti-VEGF agents, I personally would like to see trials of this drug in diabetic retinopathy and diabetic macular edema, as well as vein occlusion. **RS**

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Three Theories

(Continued from page 23)

challenging to accurately measure the ERM area.

Over time ERM contracture causes retinal striae and folds to develop often with displacement of retinal vessels. During this phase the ERM is more easily visible, with distinct edges, and leads to vision loss (*Figure 6, page 23*).²⁸ Interestingly, this has often been referred to as progression even though the ERM area rarely increases in size. ^{RS}

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Five Unresolved Questions About ERM Pathogenesis

1. Why does the epiretinal membrane not spontaneously separate more often?

2. Could it be that microglial cells growing through the microbreaks or pores create considerable anchorage and the tangential forces of ERM contracture cause the retinal striae or folding rather than separation?

3. Why do idiopathic ERMs occur primarily within the vascular arcades, even though pores in the internal limiting membrane have been documented in the peripheral retina?

4. Is it possible that the very thin or absent ILM in the paravascular retina of large vessels acts as a “fire break” that prevents extension of the ERM outside the macula in most cases?

5. Is it possible that retained vitreous segments that are primarily deposited on the posterior pole, rather than the periphery, after posterior vitreous detachment are required to initiate the ERM process? ^{RS}

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SURGICAL PEARL VIDEO

(Continued from page 13)

is ideal to keep the flap in position. Postoperative intraocular pressure spikes should not occur with this small amount of viscoelastic in the posterior segment.

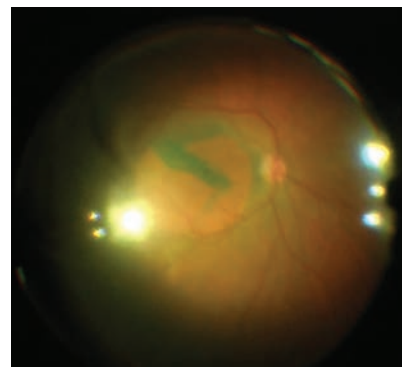


Figure 4. A well-positioned internal limiting membrane flap following air-gas exchange.

Air-fluid exchange

A nasal tilt during air-fluid exchange optimizes positioning of the temporal flap, which will drape over the hole by gravity and with the currents of remaining fluid (*Figure 4*). Here, longer-acting C_3F_8 gas may be preferred for tamponade.

This clever modification of the ILM flap maintains a hinge in eyes with a prior ILM peel to reduce the challenges of a free flap. As creative surgeons like Drs. Ali and Kaiser continue to modify the ILM flap, we can hope for a procedure to repair refractory macular holes that is more consistent and approachable than current techniques. ^{RS}

Dr. Ali is a vitreoretinal fellow at Wills Eye Hospital, Philadelphia. Dr. Kaiser is a professor of ophthalmology at Thomas Jefferson University and associate surgeon and fellowship codirector at Wills Eye Hospital.

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