A PUBLICATION BY REVIEW of Ophthalmology

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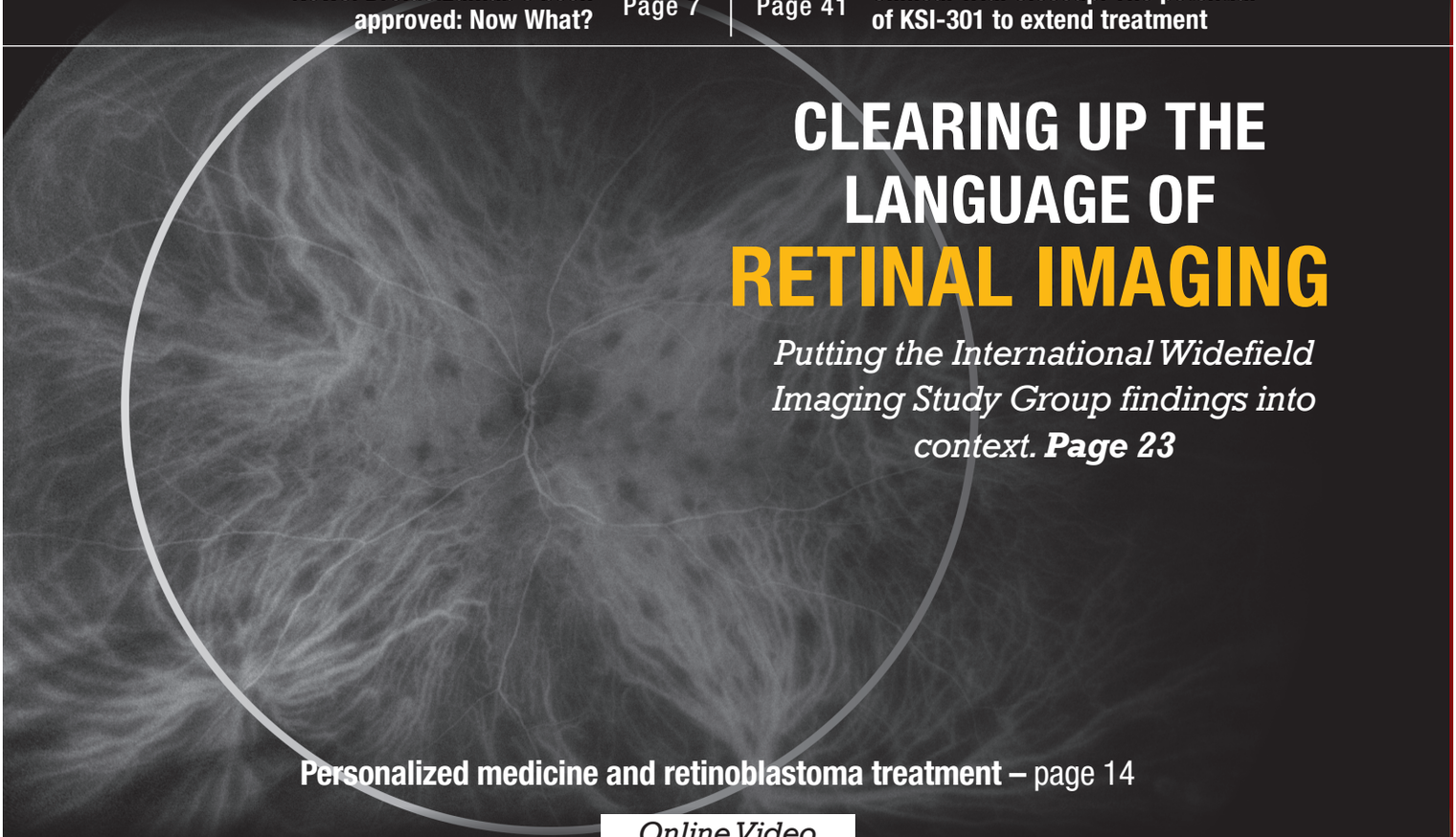

CLEARING UP THE LANGUAGE OF RETINAL IMAGING

Putting the International Widefield Imaging Study Group findings into context. ***Page 23***

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EDITORIAL

By Charles C. Wykoff, MD, PhD

Turning the tide on GA

Geographic atrophy remains the greatest unmet need in retina. The historical notion that GA progresses slowly was wrong and the concept has misled patients and their families. Numerous studies have confirmed patients afflicted with GA lose about one line of vision annually. At that rate, it doesn't take many years before the ability to drive and other quality-of-life measures are irreversibly lost.

Fortunately, data from two recent Phase II clinical trials indicate the tide may be turning. First, inhibition of complement factor 3 (C3) with pegcetacoplan resulted in statistically significant reductions in GA growth, a directionality that appeared to increase with longer drug exposure and appeared to be dose dependent.[1] Second and most recently, inhibition of C5 with avacincaptad pegol similarly resulted in statistically significant reductions in GA growth.[2] Cumulatively, through one year, these datasets indicate that GA growth may be slowed by about one third with C3 or C5 inhibition.

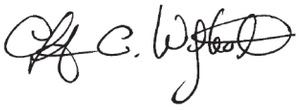
Certainly these results must be verified through additional, larger studies, which are under way. The 2018 failure of lampalizumab in Phase III was particularly disappointing, and the shock waves have lingered in our field as there remains extensive speculation that targeting GA may be just too late in the disease process to prevent vision loss. While this may yet prove to be true, armed with these recent datasets and for the benefit of our patients, I believe and hope it is not.

My conversations with patients afflicted with GA have evolved from vague comments—"There is a lot of ongoing research"—to more specific details related to these Phase II trial results.

The advent of anti-VEGF therapies for exudative diseases was the dawn of a new era. I believe we are on the edge of another leap forward with validation of complement as a viable target to slow GA progression.

Ultimately, we must pivot toward intervention at earlier stages of the disease process, such as phenotypically variable intermediate AMD, with the goal of preventing progression to late-stage AMD, including both the neovascular and GA forms; analogous to preventing progression of severe nonproliferative diabetic retinopathy to proliferative disease with pharmacotherapy.

But for now, a welcome first step toward conquering this devastating disease would be to slow the thus far inexorable march to blindness inherent in a diagnosis of GA. RS



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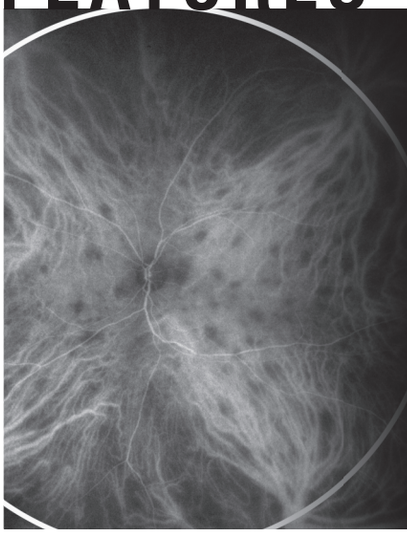
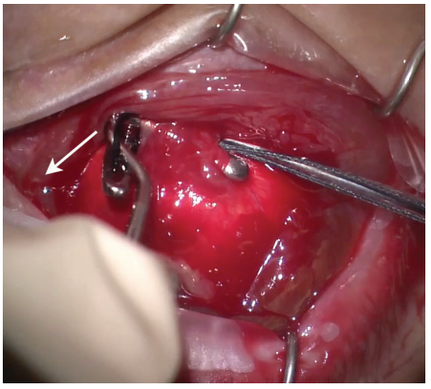
FEATURES

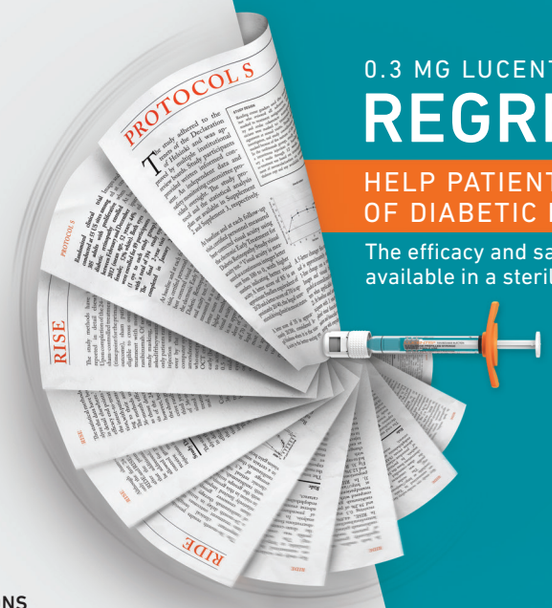


Cover Focus

ALSO INSIDE:

DEPARTMENTS





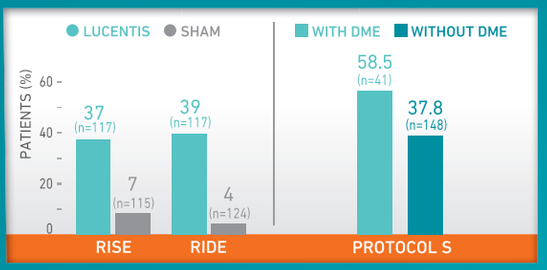
0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED[1]

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 sterile glass prefilled syringe.[1]

≥2-STEP IMPROVEMENTS AT 2 YEARS[1*]



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

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]

DME, diabetic macular edema.

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 Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017

Where the newest anti-VEGF agent fits in the exudative-disease toolbox

The long-anticipated regulatory approval of Beovu (brolucizumab, Novartis) gives retina specialists the first new anti-VEGF agent for age-related macular degeneration since the approval of Eylea (aflibercept, Regeneron Pharmaceuticals) eight years ago, and the first patients likely to get the new treatment are those with persistent fluid on optical coherence tomography after monthly treatment with the previously approved agents, an investigator of the Phase III trial tells *Retina Specialist Magazine*.

Beovu 6 mg is approved for every eight-to-12-week dosing after three monthly loading doses in neovascular AMD. At a wholesale cost of $1,850 per vial, which matches Eylea's per-vial price, the first year cost of Beovu would be $11,100 for 12-week treatment and $13,875 for eight-week treatment. For each year thereafter, cost would be $7,400 and $11,100 for 12- and eight-week regimens. In the HAWK and HARRIER trials, more than half of patients on Beovu were on the 12-week dosing interval after a year.[1] By comparison, Eylea 2 mg is approved for every four-to-eight-week dosing in nAMD after three loading doses, which equates to a yearly cost of $22,200 to $13,875.

"We chose to price it comparably with other anti-VEGF drugs indicated for wet AMD," says Patrick Mooney, vice president and head of Novartis' U.S. ophthalmology franchise. "Our strategy is to remove nonclinical barriers for payers and for physicians, and we wanted the clinical profile of the drug to stand on its own."

Arshad Khanani, MD, MA, of Reno, Nevada, a HAWK investigator, has treated multiple patients with Beovu post-approval. He says initially he used Beovu in patients with persistent subretinal or intraretinal fluid after monthly treatment with Eylea.

OCT results so far have been encouraging, he says. "If there's no subretinal fluid on OCT after a month, I'm going to try to extend the patient out to six weeks with the next Beovu injection," he says. He notes that Beovu is also suitable for treatment-naïve patients.

"I think the majority of physicians who don't have the experience with Beovu are likely to use it initially on previously treated patients with persistent subretinal or intraretinal fluid on four-to-five-week treatment with Eylea," Dr. Khanani says.

He notes the HAWK and HARRIER trials reported that Beovu was more effective than Eylea at resolving subretinal and/or intraretinal fluid as well as subretinal pigment epithelium fluid. "Once they see the efficacy in terms of drying the retina and that they can actually increase the interval between treatments, then they're going to start using Beovu more in treatment-naïve patients," he says.

At first some physicians may have been reluctant to use Beovu because it doesn't have a J-code, but Novartis does have support programs to deal with coverage lapses, Dr. Khanani says. A permanent J-code has already been assigned by the Centers for Medicare and Medicaid Services and it will go in effect in January 2020.

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IN BRIEF

Optos has launched **Silverstone**, an imaging system combining ultra-widefield retinal imaging with integrated, image-guided, swept-source optical coherence tomography. It produces a 200-degree, single-capture Optomap image with guided OCT, enabling advanced OCT imaging from the posterior pole to the far periphery of the retina, providing UWF-guided multimodal imaging.

A **Bausch Health** affiliate has acquired an exclusive license for the commercialization and development of **Clearside Biomedical's Xipere** triamcinolone acetonide suprachoroidal injectable suspension in the United States and Canada. Xipere is a proprietary suspension of triamcinolone acetonide formulated for suprachoroidal administration via Clearside's proprietary SCS Microinjector.

Bausch + Lomb has launched **PreserVision AREDS 2 Formula** mini-gel eye vitamins, replacing PreserVision AREDS 2 Formula soft gels. The vitamins contain the same National Eye Institute-recommended formula for moderate to advanced age-related macular degeneration.

Aerie Pharmaceuticals has completed patient enrollment in its Phase II clinical trial of **AR-1105** for macular edema due to retinal vein occlusion. AR-1105 is an investigational sustained-release, bio-erodible intravitreal implant containing dexamethasone. The trial will evaluate safety and efficacy of AR-1105 at six months.

Study upends conventional thinking on retinal artery occlusion, stroke

Occlusion of the retinal artery has been thought to be a predictor of stroke, but an analysis of patients with diagnosed retinal artery occlusion at the Cleveland Clinic has found that their risk of stroke is about the same as the general population.

"Subsequent hemispheric stroke is rare with or following retinal artery occlusion," says David Laczynski, MD, a vascular surgeon at the Cleveland Clinic. He reported the results at the annual meeting of the Midwestern Vascular Surgery Society in Chicago. "We do caution that large database studies may be overestimating the risk of stroke after RAO," he says, citing studies that have reported stroke rates of up to 20 percent at one year.[1]

The study evaluated 221 patients whose RAO was confirmed with fluorescein angiography from 2004 to 2018 at the Cleveland Clinic Cole Eye Institute.[2] The study population is the largest series in RAO ever reported, he says.

The impetus of the study was to use the eye center to evaluate the institution's experience with RAO, Dr. Laczynski says. "We were specifically concerned with looking at confirmed, symptomatic RAO with the risk of subsequent stroke," he says. The study's hypothesis was that RAO isn't associated with an increased risk of stroke.

The average age of patients was 66 years. With a median follow-up of 2.2 years, the stroke rate was 2.3 percent (n=5), with four of the strokes occurring at the time of RAO and one at 1.2 years later. Only one stroke patient had greater than 50 percent stenosis of the carotid artery. The rate of stroke, death or myocardial infarction was 10 percent (n=22), Dr. Laczynski says. When concurrent ischemic events were excluded, the stroke rate was less than 1 percent.

"Sixty-three percent of patients (n=141) had carotid imaging, but only 14.2 percent (n=20) had more than 50 percent stenosis of the carotid artery," Dr. Laczynski says. "Ten patients had carotid intervention."

Among study limitations Dr. Laczynski points out were its single-center, retrospective nature and that not all patients had carotid artery imaging. "We cannot make any conclusion in regard to RAO and carotid artery disease," Dr. Laczynski says.

Quotable

The rate of stroke, death or myocardial infarction was 10 percent. When concurrent ischemic events were excluded, the stroke rate was less than 1 percent.

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1. Chang YS, Jan RL, Weng SF, et al Retinal artery occlusion and the 3-year risk of stroke in Taiwan: a nationwide population-based study. Am J Ophthalmol. 2012;154:645-652.
2. Laczynski DJ, Lyden SP, Gallop J, Bena J, Caputo FJ. Retinal artery occlusion does not portend an increased risk of stroke. Abstract presented at Midwestern Vascular 2019; Chicago, Ill.; September 13, 2019.

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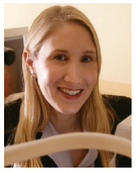
Melanoma? Or pseudomelanoma?

A patient develops two rare lesions in the same eye.

By Mai Tsukikawa, MD, Debarshi Mustafi, MD, PhD, and Andrew W. Stacey, MD



Department Editor
Lisa C. Olmos de Koo, MD, MBA

On B-scan ultrasound, the lesion appeared as a dome-shaped mass with medium internal reflectivity, measuring 9 x 7.5 mm with a thickness of 3.4 mm.

A 77-year-old male was referred to the ocular oncology service at the University of Washington Eye Institute by his primary care physician for evaluation of a choroidal lesion in his left eye found incidentally on imaging. An MRI brain scan, ordered for unrelated dysphagia, showed an ovoid hyperintense lesion in his left globe.

Examination and findings

The patient was last seen six years earlier by an ophthalmologist, who noted a choroidal nevus in the superonasal periphery of the left eye. The patient's ocular history was notable for pseduophakia in both eyes, and his medical history was significant for hypertension and type 2 diabetes.

Upon evaluation at our clinic, visual acuity was 20/20 in both eyes. Intraocular pressures were normal, and pupils equal, round and reactive with no relative afferent pupillary defect. Extraocular motility was full, as were confrontational visual fields in both eyes. Slit-lamp examination was within normal limits with a posterior chamber intraocular lens in each eye.

The dilated fundus exam in the left eye was notable for a pigmented choroidal lesion in the superonasal periphery with central lipofuscin and associated subretinal fluid. On B-scan ultrasound, the lesion appeared as a dome-shaped mass with medium internal reflectivity, measuring 9 x 7.5 mm with a thickness of 3.4 mm.

Work-up and surgery

Lesion growth, lipofuscin and subretinal fluid were consistent with a diagnosis of choroidal melanoma due to malignant transformation of a choroidal nevus. CT-scan of the chest, abdomen, and pelvis didn't show any evidence of visceral metastases or lymphadenopathy. The patient underwent an operation to have tantalum clips placed and had proton beam radiotherapy. During the surgery, a trans-vitreous choroidal fine-needle aspiration was obtained. Castle gene expression profile showed that the lesion was Class 1A, portending a 98 percent chance of metastasis-free survival at five years.

Six months after completing proton beam therapy, the patient returned with vision decreased to light perception in the

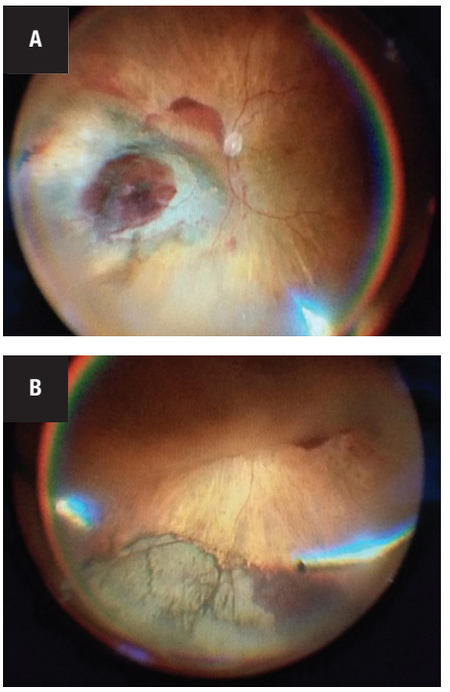


Figure 1. Operating room photographs taken during pars plana vitrectomy for non-clearing vitreous hemorrhage show (A) a large choroidal mass in the superonasal periphery abutting the optic nerve with shallow areas of subretinal fluid extending inferiorly and toward the nerve, identified as the choroidal melanoma, and (B) a secondary elevated choroidal mass inferiorly spanning from 5 to 7 o'clock with a mottled brownish-yellowish appearance, diagnosed as a peripheral exudative hemorrhagic chorioretinopathy lesion.

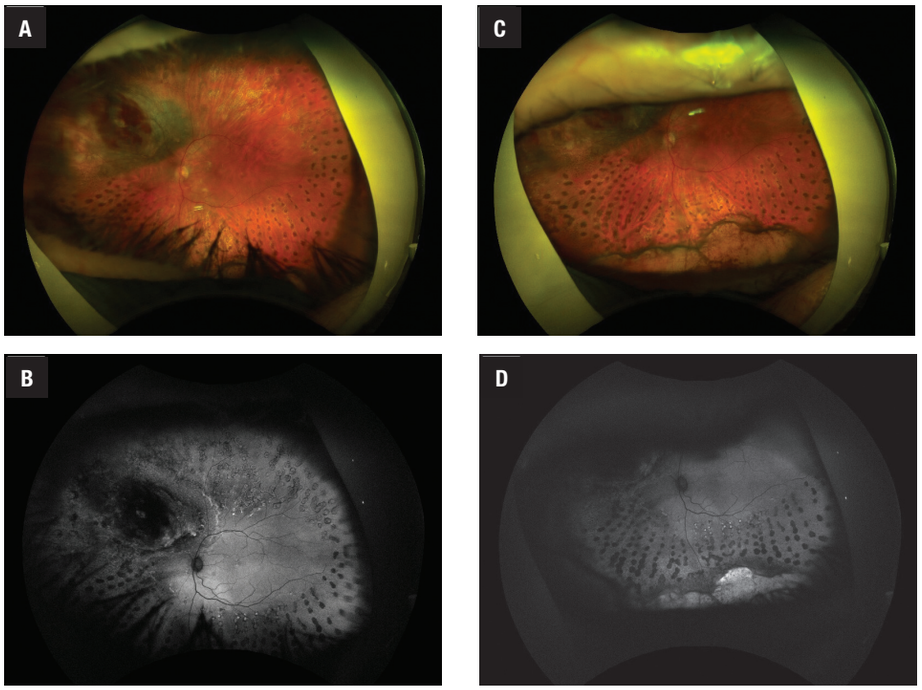


Figure 2. Optos color fundus photograph and fundus autofluorescence at two months postoperatively demonstrate the choroidal melanoma superonasally (A and B) and the peripheral exudative hemorrhagic chorioretinopathy lesion inferiorly (C and D).

left eye. Examination revealed no view to the posterior pole, and a dense vitreous hemorrhage precluded ophthalmoscopic examination of the melanoma, which was stable on B-scan. The vitreous hemorrhage was presumed to be due to radiation retinopathy and the patient was referred to the retina service for consideration of pars plana vitrectomy and pan-retinal photocoagulation.

A second elevated mass

The patient was taken to the operating room for pars plana vitrectomy. A large mass of dehemoglobinized vitreous hemorrhage was present in the central vitreous, which was cleared and shaved into the periphery for 360 degrees. The choroidal melanoma was identified as a large choroidal mass in the superonasal periphery abutting the optic nerve with shallow areas of subretinal fluid extending inferiorly and toward the nerve (*Figure 1A*).

Unexpectedly, we noted a second elevated choroidal mass inferiorly, spanning from 5 to 7 o'clock with a mottled brownish-yellowish appearance (*Figure 1B*). This was clinically diagnosed as peripheral exudative hemorrhagic chorioretinopathy (PEHCR). We applied a 360-degree endolaser peripheral panretinal photocoagulation to treat presumed radiation retinopathy, sparing the surfaces of the two mass lesions. At the conclusion of the case, we injected a 0.05 mL of intravitreal bevacizumab (Avastin, Genentech/Roche) to treat the presumed active choroidal neovascular membrane.

The PEHCR lesion was likely the source of the patient's large vitreous hemorrhage. At his most recent visit at two months postoperatively, vision was 20/20 in both eyes. Color fundus photos and fundus autofluorescence of the left eye demonstrated the choroidal melanoma superonasally (*Figure 2A and B*) and the PEHCR lesion inferiorly (*Figure 2C and D*). B-scan ultrasound of

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Dr. Olmos de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington in Seattle, where Dr. Stacey is an assistant professor of ophthalmology specializing in ocular oncology. Dr. Tsukikawa is an ophthalmology resident and Dr. Mustafi is a retina fellow.

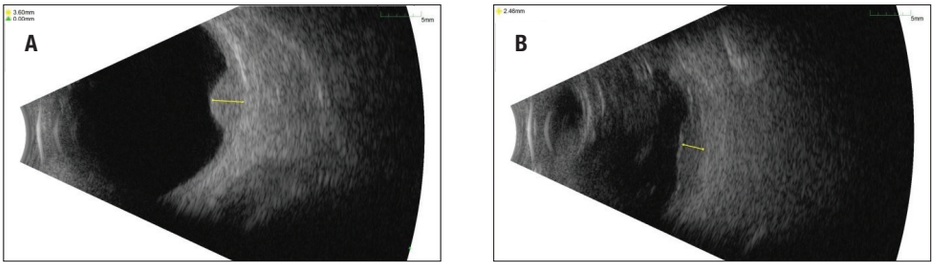


Figure 3. B-scan ultrasound at two months postoperatively reveals a (A) dome-shaped choroidal mass superonasally at 10 o'clock with maximal height 3.60 mm, and (B) a diffusely corrugated choroidal mass inferiorly at 6 o'clock with maximal height of 2.46 mm.

the two lesions showed a dome shaped choroidal mass superonasally at 10 o'clock with maximal height of 3.6 mm (*Figure 3A*), and a diffusely corrugated choroidal mass inferiorly at 6 o'clock with maximal height of 2.46 mm (*Figure 3B*).

Features of PEHCR

PEHCR is a retinal degenerative process featuring subretinal or subretinal pigment epithelium hemorrhage or exudation. These lesions were first reported in 1961, when Algernon Reese, MD, and Ira Jones, MD, described 34 cases of hematomas under the RPE, of which four cases were peripheral to the macular region.[1] In 1980, William Annesley Jr., MD, characterized 32 lesions with blood in the subretinal or sub-RPE space, which he termed "peripheral exudative hemorrhagic chorioretinopathy."[2]

PEHCR is often misinterpreted as an intraocular tumor, in particular choroidal melanoma. Jerry Shields, MD, and colleagues found that 1,739 (14 percent) of 12,000 patients who were referred for evaluation of presumed uveal melanoma actually proved to have a pseudomelanoma.[3] In this series, PEHCR (13 percent) was second only to choroidal nevus (49 percent) as the leading category of pseudomelanomas.

In a subsequent study, Carol Shields, MD, and colleagues further investigated the features of PEHCR in 173 eyes of 146 patients referred with the diagnosis of choroidal melanoma.[4] The mean patient age was 80 years, and most patients were Caucasian (99 percent) and female (67 percent). The lesions were bilateral in 31 percent.

Patients with PEHCR consistently have systemic hypertension. Dr. Carol Shields and colleagues reported 51 percent of patients in their series had hypertension.[4] Dr. Annesley reported 44.4 percent of 27 patients had it,[2] and a Swiss study reported 55 percent of 40 patients had hypertension.[5]

In the series by Dr. Carol Shields and colleagues, a high percentage of patients (42 percent) were asymptomatic, 37 percent had decreased vision and 20 percent had flashes/floaters.[4] Thirty-six eyes (21 percent) had decreased visual acuity related to the PEHCR lesion, which was associated with the following presenting symptoms: vitreous hemorrhage in 24 eyes (14 percent); subretinal hemorrhage extending to the macula in eight eyes (5 percent); and subretinal fluid extending to the macula in four eyes (2 percent).

PEHCR lesions are found most commonly in the temporal quadrant, specifically in the inferotemporal quadrant and between the equator and the ora serrata.[2,4,5] This is in contrast to choroidal melanomas, which are most commonly located at the macula or between the macula and the equator.[6]

On ocular ultrasound, PEHCR lesions appear as dome or plateau-shaped elevated lesions. In Dr. Carol Shields' series, the mean basal dimension was 10.1 mm and the mean thickness was 3 mm.[4] The lesions

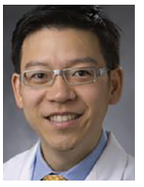
(Continued on page 27)

PEHCR lesions are found most commonly in the temporal quadrant, specifically in the inferotemporal quadrant and between the equator and the ora serrata.

Never use two steps when one will do

Step-saving tips when isolating rectus muscles and performing membrane peeling.

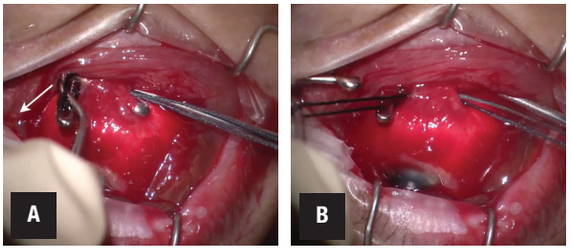
By David R.P. Almeida, MD, MBA, PhD



Department Editor
Paul Hahn, MD, PhD

The most valuable of all talents is that of never using two words when one will do.
—Thomas Jefferson

Surgical maneuvers are akin to language and, like the Thomas Jefferson quote above, reminds us that succinct communication is always preferred. The same can be said for surgical procedures: Efficiency by means of eliminating redundancy is our manifesto, and here are two examples you can incorporate into your surgical cases right away.



One-step rectus muscle suture isolation. After a muscle hook has been used to isolate the rectus muscle (left hand), the suture is passed from the opposite direction (right hand). The back knuckle of the muscle hook is used to engage the suture (A) and is pulled away, completing looping of the muscle (B). This negates the need for an additional step to grasp the rectus muscle suture.

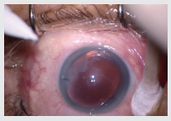
Isolating rectus muscles

Whether you are looping muscles in preparation for placement of a scleral buckle or isolating rectus muscles for more advanced maneuvers like choroidal drainage, notice how I isolate the inferior rectus in the first video segment.

After I isolate the rectus muscle with a Green muscle hook and loop the muscle with a heavy silk suture, I slide the muscle hook backward and pull out the suture at the same time that I remove the muscle hook. This is very simple but speaks to constantly looking for opportunities to improve efficiency.

As the residents and fellows who work with me know, I'm obsessed with eliminating surgical redundancy. Never use two steps when one will do. Economical surgical maneuvers will dramatically improve your efficiency in the operating room.

View the Video



Dr. Almeida demonstrates simple steps to improve surgical efficiency during scleral buckling and membrane peeling. Available at: http://bit.ly/VideoPearl_014

Membrane peeling

Next, we apply the same theme where I use one instrument instead of two for membrane peeling. For epimacular membranes, I favor a pinch-and-peel technique. However, with proliferative membranes in the detached retina, pinch-and-peel is sometimes awkward due to the presence of subretinal fluid, corrugations and/or folds in detached retina.

As you see in the second part of the video, you can use end-grasping (internal limiting membrane-style) forceps in the closed position and use the closed end to abrade membranes to release them from detached retina. This provides you with an easy technique to elevate a membrane edge. You can then grasp and peel in the usual fashion.

Although I'm a fan of the Tano diamond dusted membrane scraper and the Alcon Finesse Flex Loop, both of which can be used to initiate membrane dissection, you can also do this with end-grasping forceps in the closed position. This aids membranectomy efficiency without the use of additional instruments.

Bios

Dr. Hahn is a vitreoretinal surgeon at NJ Retina in Teaneck, N.J.
Dr. Almeida is a vitreoretinal surgeon at Erie Retinal Surgery, Erie, Pa.

DISCLOSURES: Dr. Hahn has no relevant disclosures.

Dr. Almeida disclosed relationships with Alcon, Allergan, Bayer, Genentech, Novartis and Regeneron Pharmaceuticals, and is cofounder and equity holder in Citrus Therapeutics.

Personalized medicine and retinoblastoma treatment

Globe-salvaging therapies are minimizing the need for enucleation for the most common primary intraocular malignancy of childhood.

Victor M. Villegas, MD

Timothy G. Murray, MD, MBA, FACS

By Victor M. Villegas, MD, and Timothy G. Murray, MD, MBA, FACS

Take-home points

- Transitioning to globe-salvaging therapies has been universally adopted with the focus remaining on decreased morbidity and mortality.
- Treatments for retinoblastoma are trending toward targeted primary therapy with selective intra-arterial and intravitreal chemotherapy.
- The classic three-drug systemic treatment—carboplatin, vincristine and etoposide—has been linked with significant morbidity and routinely requires multiple cycles.
- Intravitreal chemotherapy has shown promise as a treatment, but further studies are needed to better evaluate its long-term safety.

Bios

Dr. Villegas is with Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami; the department of ophthalmology at the University of Puerto Rico, San Juan; and the department of surgery at Ponce Health Sciences University, Ponce, Puerto Rico.

Dr. Murray is with Murray Ocular Oncology and Retina (MOOR), Miami.

DISCLOSURES:
Dr. Villegas and Murray have no relevant financial relationships to disclose.

Retinoblastoma continues to be the most common primary intraocular malignancy of childhood. However, enucleation continues to be the international gold standard of management. During the last 20 years, globe-salvaging therapies with chemoreduction and focal consolidation have significantly improved the morbidity associated with retinoblastoma RB therapy.

Still, some developing countries with limited access to medical care continue to struggle with the high morbidity and mortality associated to the natural course of the disease.[1,2] Today, novel treatments for advanced disease are actively being investigated to minimize the need of enucleation and limit the toxicities associated to therapy. This article reviews the most current clinical pearls in the management of retinoblastoma.

Retinoblastoma (RB) affects one in 15,000 to 20,000 live births.[1] Early diagnosis is of critical importance because small tumors have the best prognosis. Leukocoria is the most common sign at initial presentation (*Figure 1*).[1] However, small or peripheral tumors may not alter the red-reflex. Sensory strabismus is the second most common sign.[2]

Focus on local treatments

Therapies for RB have dramatically ad-

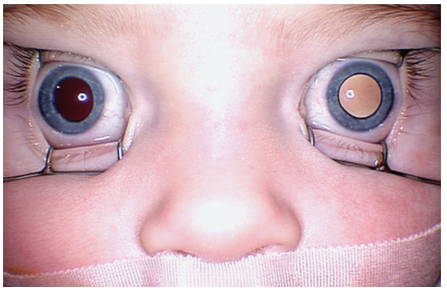


Figure 1. Child with germline RB1 mutation and bilateral retinoblastoma. Note the asymmetric red-reflex.

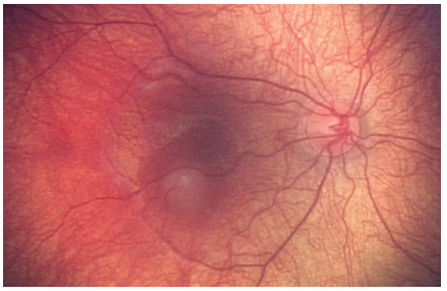


Figure 2. Small macular retinoblastoma in the right eye amenable to primary focal ablation.

vanced during the last 10 years. A significant trend toward targeted primary therapy with selective intra-arterial and intravitreal chemotherapy is currently under way. Technological changes and strategies focus on local treatments due to decreased morbidity to patients and excellent tumor response. New treatments are providing new hope to patients, especially to those with the most severe disease.

Management of RB tumors requires a multidisciplinary approach that may include an ocular oncologist, pediatric oncologist, pediatric ophthalmologist, pediatrician, interventional radiologist and ocular pathologist. Individualized treatment, considering factors such as the International Classification (IC) of RB, laterality, location of tumors, age of patient, family history and prior treatment must be considered,[1,3] although RB treatment is aimed at child survival. Globe salvage and preservation of vision are important secondary goals. Early diagnosis remains the most crucial step in decreasing morbidity and mortality.[2]

Treatment of small tumors (*Figure 2*) may only require transpupillary thermotherapy.[4] Laser treatments may be repeated monthly until complete tumor regression is documented.[5] Close follow-up with patients is important to monitor for recurrence. If recurrence is detected, systemic or intra-arterial chemotherapy may be considered.

Chemotherapy and chemoreduction

The classic three-drug systemic treatment (carboplatin, vincristine and etoposide) has been associated with significant morbidity, and it routinely requires multiple cycles. Bone marrow suppression, ototoxicity, nephrotoxicity and risk of induction of secondary cancers have been reported.[6-7] Controversy continues to surround the role of systemic chemotherapy in the prevention of trilateral RB.[8-9] The combination of systemic and/or intra-arterial chemotherapy with focal ablative treatments has been shown to have better globe salvage rates than chemotherapy alone in both early and advanced RB.[10-13]

A recent study on macular retinoblastoma outcomes showed that chemoreduction with transpupillary thermotherapy of both foveal and extrafoveal tumors achieve control in 83 percent of R-E group V tumors.[14] All tumors less than R-E group V achieved 100-percent control. Despite ablative foveal laser treatment, 56 percent of eyes had better than 20/80 visual acuity.

Enucleation remains the standard treatment of group E RB tumors.[15] Histopathologic analysis may determine if adjuvant treatment is necessary depending on high-risk criteria at the time of enucleation.[16] Adjuvant therapy postenucleation has been shown to decrease metastasis in advanced RB from 24 to 4 percent of children.[17]

Intra-arterial chemotherapy

Physicians in Japan revolutionized the treatment of RB by infusing melphalan directly into the ophthalmic artery.[18] The initial technique consisted of catheterization of the internal carotid artery and occlusion of a micro-balloon distal to the ophthalmic artery. During the temporary occlusion, melphalan was infused into the ophthalmic artery. The study involved 563 intra-arterial chemotherapy procedures in 187 patients with no reported serious complications, including stroke. The most common complications were mild transient bradycardia, periorbital erythema and swelling.[18]

Following the initial publication, many large centers had significant interest in developing the technique in patients

A recent study showed that chemo-reduction with transpupillary thermo-therapy of both foveal and extra-foveal tumors achieved control in 83 percent of R-E group V tumors.

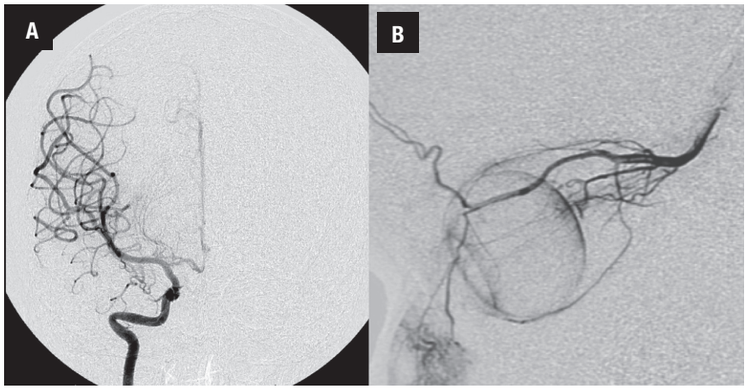


Figure 3. Digitally subtracted selective arteriogram images show internal carotid artery arteriogram without balloon occlusion (A) and selective ophthalmic artery arteriogram prior to chemotherapy infusion (B).

Sequential intravenous chemotherapy followed by intra-arterial chemotherapy (bridge chemotherapy) for young infants with retinoblastoma may be considered in cases were cannulation of the ophthalmic artery is not possible.

with advanced RB. Subsequently, David Abramson, MD, and associates at Memorial Sloan-Kettering Cancer Center developed a technique that allowed treatment without the need to occlude the distal cerebral blood flow at the time of infusion (*Figure 3*).[19]

Recent studies have validated the efficacy of intra-arterial chemotherapy.[20-22] Interest in intra-arterial delivery of other chemotherapeutic agents has prompted various small studies. This strategy has been investigated to avoid melphalan dose restriction during bilateral therapy. Jasmine Francis, MD, and colleagues at Memorial Sloan-Kettering reported in 2012 that the use of single-agent carboplatin at doses ranging from 25 to 40 mg, and cumulative doses from 25 to 100 mg, in three cases where high-dose melphalan was needed in the contralateral eye and systemic toxicity limited the use of melphalan to one eye.[23] They reported tumor regression with as little as one cycle and no systemic adverse effects.

Similar results have been reported with intra-arterial infusion of both carboplatin and topotecan.[24] In addition, analysis of electroretinogram (ERG) responses following infusions containing carboplatin only and carboplatin with topotecan revealed no statistically significant change.[23-24]

Three-drug intra-arterial treatment

Most recently, a trend toward three-drug intra-arterial treatment (carboplatin, melphalan and topotecan) has been reported.[25] Twenty-six eyes of 25 patients received the three-drug chemotherapy for treatment of advanced retinoblastoma. Dose ranges were 2.5 to 7.5 mg of melphalan, 0.3 to 0.6 mg of topotecan and 25 to 50 mg of carboplatin. Median infusions per eye were two (range: two to four). The Kaplan-Meier estimate of ocular survival at 24 months was 75 percent. ERG showed improvement greater than 25 µV in four eyes (15 percent), loss greater than 25 µV in 12 eyes (46 percent) and no change greater than 25 µV in 10 eyes (39 percent).

Other large studies have also reported successful treatment with this regimen.[21] These findings suggest that selective intra-arterial combination therapy with carboplatin and melphalan is effective in the treatment of RB and decreases the toxic window during treatment especially in patients that need bilateral therapy.

Sequential intravenous chemotherapy followed by intra-arterial chemotherapy (bridge chemotherapy) for young infants with retinoblastoma may be considered when cannulation of the ophthalmic artery isn't possible.[26] Further studies will elucidate the optimal timing for bridging.

Intravitreal chemotherapy

The significant tumoricidal effects reported with intra-arterial melphalan generated enthusiasm to study intravitreal delivery for vitreous seeding. However, the potential for tumor dissemination through the needle tract following intravitreal penetration has limited its use.

In 2012 researchers at Jules-Gonin Eye Hospital in Switzerland reported the first clinically documented case series of patients with retinoblastoma treated with intravitreal melphalan.[27] The study included 122 intravitreal injections of melphalan in 23 eyes that had significant active vitreous seeding after primary therapy. Globe

retention was achieved in 87 percent (20 of 23) of patients. Despite the confounding effects of concomitant chemotherapy, the study showed that intravitreal melphalan achieved unprecedented control of vitreous seeding.[27]

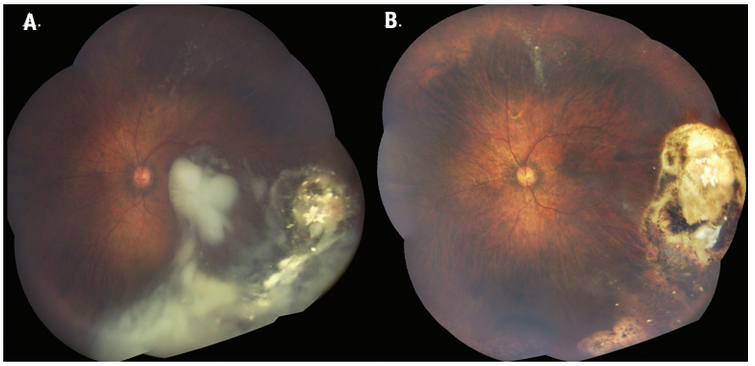


Figure 4. Initial presentation of retinoblastoma with globular seeding (A) and at follow-up after intra-arterial chemotherapy and two adjuvant intravitreal melphalan injections (B).

A recent bi-institutional cohort study evaluated the vitreous seed response after 475 intravitreal melphalan injections.[28] The study included 87 eyes treated weekly (median dose, 30 µg) with a median of five treatments per eye (range, one to 12 times). The two-year Kaplan-Meier estimates for ocular survival and patient survival were 90.4 percent and 100 percent, respectively. Other authors have also reported on the efficacy of intravitreal melphalan for the treatment of RB (*Figure 4*).[29-31]

The risk of tumor dissemination after intravitreal injection was evaluated in a 2013 study of 304 patients following therapeutic intravitreal melphalan injections for RB.[32] Only one patient had extraocular tumor spread.

The proportion of subjects with extraocular tumor spread potentially due to intravitreal treatment in these combined reports was 0.007 (95% confidence interval, range of 0.0008 to 0.0236), with a mean follow-up of 72.1 months. No reports of tumor spread occurred in a subset of 61 patients receiving intravitreal treatment via safety-enhancing injection techniques (347 injections, 19.6 months mean follow-up). This study concluded that RB metastasis following intravitreal therapy is rare and shouldn't preclude its clinical use in appropriately selected cases.

Intravitreal chemotherapy safety

Data regarding toxicity of intravitreal melphalan continues to be limited. A 2014 study that evaluated retinal and systemic toxicity of intravitreal melphalan in a rabbit model concluded that weekly injections of 30 µg of melphalan can result in a decreased ERG response.[33] Previous studies have also shown that 50-µg of intravitreal melphalan is toxic to the eye with persistent hypotonia and phthisis bulbi.[31] In contrast, 20/40 visual acuity has been reported in a patient that received four doses (30, 30, 30 and 20 µg) of intravitreal melphalan with no change in ERG amplitudes before and after therapy.[30]

Effective intravitreal combination of melphalan (40 µg in 0.04 mL of diluent) and topotecan (8 to 20 µg in 0.04 mL of balanced salt solution) has also recently been reported in nine eyes.[34] In the study, no cases of episcleral or orbital retinoblastoma extension or remote retinoblastoma metastasis were reported. There was no change in the A and B waves of bright-flash ERG.

Most recently, a study published this year by Dr. Abramson and colleagues showed that intravitreal chemotherapy may be effective in primary treatment non-vitreous disease, including subretinal seeding, anterior segment dissemination and select retinal tumors.[35]

(Continued on page 21)

The adoption of specific guidelines for intravitreal treatment case selection and additional data on potential ocular toxicity remain essential to enable a more widespread use of chemotherapy.

START WITH
THE POWER OF EYLEA

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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Trust ≈8 Years of Extensive Clinical Experience and the Integrity of Data From Large, Well-Controlled Trials[1]

EYLEA IS THE

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*IBM Truven MarketScan data: Number of injections administered from Q4 2017 through Q3 2018; data on file.

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AN ESTIMATED

≈9 MILLION DOSES ADMINISTERED TO ≈790,000 EYES TREATED SINCE LAUNCH[2]

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ADVERSE REACTIONS

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

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

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

09/2019
EYL.19.09.0044

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS.

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

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

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

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

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

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

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

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

REGENERON

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

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

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

EYL.19.07.0306

(Continued from page 17)

Further studies are required to assess the safety of long-term intravitreal therapy and to better delineate its role in the management of retinoblastoma. The adoption of specific guidelines for intravitreal treatment case selection and additional data on potential ocular toxicity remain essential to enable a more widespread use of this treatment.

Periocular chemotherapy

Focal therapies aim at increasing the tumoricidal effects in RB-affected tissues while minimizing systemic toxicity. Multiple researchers have investigated periocular chemotherapy as adjuvant to systemic, intra-arterial and intravitreal chemotherapy.[36-39]

Treatment-associated toxicities may include transient periorbital edema, strabismus, optic neuropathy, periocular inflammation and fat atrophy. Inflammation associated with periocular agents, particularly carboplatin, has limited their widespread use in children with RB. Periocular topotecan hydrochloride has also been investigated as adjuvant therapy in patients with RB with minimal toxicity.[40]

A study by one of us (TGM) and colleagues evaluated the effects of intravitreal and subconjunctival melphalan on tumor burden, hypoxia and vasculature in a transgenic mouse retinoblastoma model. We reported a significant decline in hypoxia at one week following intravitreal injection and after maximum dosage of subconjunctival melphalan.[41] This study found a significant decrease in tumor burden following serial subconjunctival injections of melphalan, showing an 86 percent reduction. No toxicities were seen on histology following treatments.

Prospective studies are needed to assess the role of periocular chemotherapies for the treatment of RB. Nevertheless, the trend toward direct intravitreal therapy has limited the widespread use of periocular treatments.

Shifting treatment trends

Over the last three decades, major shifts in therapy have occurred. Historically, enucleation was the treatment of choice before the 1980s, followed by transition to external beam radiotherapy (EBRT) through the mid 1990s, moving to systemic chemotherapy with laser tumor ablation until 2010, when intra-arterial chemotherapy was instituted at major ocular oncology centers. Currently, each of these modalities continues to have a role in treatment, with the major focus remaining cure of the retinoblastoma cancer, avoidance of mortality and an evolving recognition of the ability to preserve function within these complex eyes.

Sadly, for primary enucleation therapy within the United States, recent reports by Carol Shields, MD, and David Abramson, MD, have noted a metastatic incidence over the last decade approaching 4 percent. Addressing this concern, our group has used chemotherapy (both systemically and intra-arterially) before enucleation to lower metastatic risk and ultimately mortality. With this targeted approach, our metastatic rate is below 1 percent, suggesting a benefit to this targeted approach. Clearly, early detection, integration of advanced therapies and serial screening for our retinoblastoma patients are critical.

Bottom line

Ocular oncology is currently navigating through a therapeutic revolution that is geared toward the application of focal individualized therapies. The majority of these changes in management have happened without clinical trials. Clinical experience remains the most important tool in the management of patients with RB. We anticipate large randomized clinical trials that will better delineate how to use the available therapeutic options more efficiently.

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Prospective studies are needed to evaluate periocular chemotherapies for the treatment of RB. The trend toward direct intravitreal therapy has limited the widespread use of periocular treatments.

Viral vectors are being investigated as a possible mechanism to directly target retinoblastoma cells. Other developments include the application of extended-release implants to deliver chemotherapeutic agents. directly to the globe.

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Technological frontiers in ocular oncology

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Cover Focus

Clearing up the language of retinal imaging

A review of the International Widefield Imaging Study Group recommendations for a terminology to describe image captures from various modalities.

By Netan Choudhry, MD, FRCSC

Take-home points

- Definitions bring consistency to the use of *widefield* and *ultra-widefield* to describe retinal images.
- The four vortex veins provide anatomical landmarks that are integral to the definitions the consensus group agreed on.
- The definitions are predicated on the agreed-upon definition of *field of view* centered on the macula.
- Going forward, the study group will continue to evaluate new technologies.

Netan Choudhry, MD, FRCS

The recommendations for terminology for ophthalmic imaging by the International Widefield Imaging Study Group, published online in October in *Ophthalmology Retina*,[1] had been highly anticipated.

As the lead author of those findings, *Retina Specialist Magazine* has asked me to provide some context on what those findings mean for us in the clinic.

This study group came together because over the last several years a great deal of confusion in the literature has surrounded the terminology for describing images captured by the various modalities we have at our disposal: color fundus photography; fluorescein angiography; autofluorescence; indocyanine green angiography; optical coherence tomography (OCT B-scans); and *en face* OCT angiography.

Most prominent among these are the terms *widefield* and *ultra-widefield*. Manufacturers have used their own terminology and that has had some influence on the nomenclature researchers have used in their papers. However, this is an area in which there's never been a consensus of how we define these terms. Reaching that consensus was the goal of this group.

Examples of unclear terminology

Here are two examples of the confusion that has existed. An article that reports on an OCT scan that doesn't go beyond the arcades to acquire a full view of the retina and uses the term *widefield enface imaging* isn't really giving us the full perspective. The reader may then associate the term *widefield* with that field of view, but the image doesn't even show half of the retina, or maybe even more than half.

Or take an OCT that doesn't show a single line scan of a lesion in the far periphery. Would that be considered a *widefield* or *ultra-widefield* view, or neither? So the question is, how do we unify our language so we're all saying the same thing in the literature?

Key definitions

The anatomical features integral to the IWFISG's recommendations are the four

Bio

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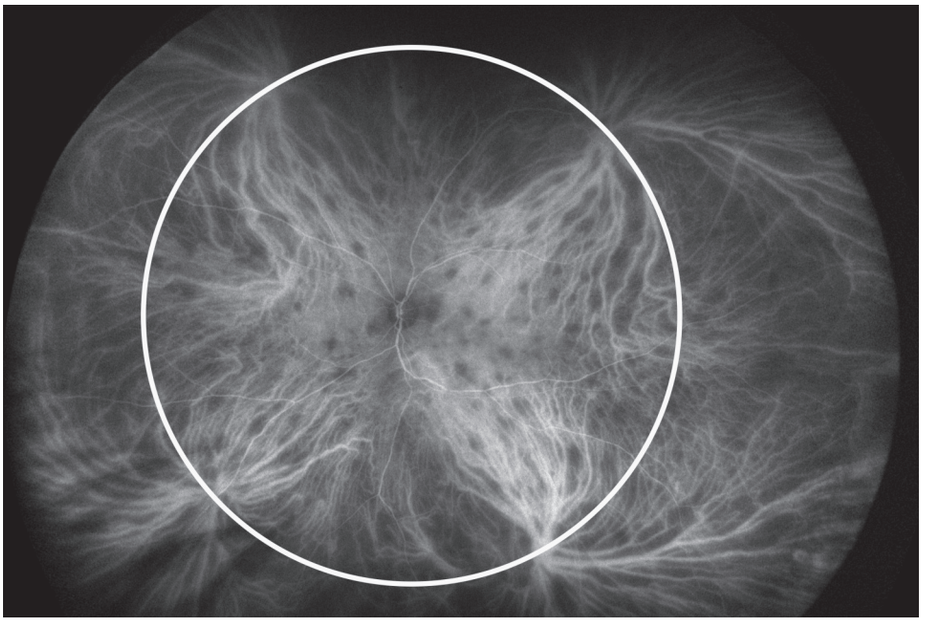
DISCLOSURES:

Dr. Choudhry disclosed he is a consultant for Topcon, Optos, Bayer, Allergan, Novartis, Carl Zeiss Meditec and Ellex, and receives research equipment from Topcon, Optos and Carl Zeiss Meditec.



Single-capture ultra-widefield image of an eye with birdshot dhoroiditis The white circle marks the locations of vortex vein ampullae in all four quadrants. The International Widefield Imaging Study Group definition of an UWF image is one that includes retinal anatomy anterior to the vortex vein ampullae (beyond the circle) in all four quadrants. (Courtesy Optos)

For optical coherence tomography angiography, widefield is defined as retina in all four quadrants and includes the retina up to the posterior edge of vortex vein ampullae.

vortex veins that most, although not all, patients have. The definitions for fundus photography, angiography and AF the group has suggested are:

- *Posterior pole*—retina within the arcades and just slightly beyond them.
- *Midperiphery*—region of the retina up to the posterior edge of the vortex vein ampulla.
- *Far periphery*—region of the retina anterior to the vortex vein ampulla.
- *Widefield*—single-capture image centered on the fovea and capture the retina in all four quadrants, posterior to and including the vortex vein ampullae.
- *Ultra-widefield*—single-capture view of the retina in the far periphery in all four quadrants.
- *Panretinal*—a single-capture, 360-degree ora-to-ora view of the retina.

For OCT, the definitions vary somewhat. For OCT B-scans, the following principles apply:

- They're used primarily for cross-sectional examination of the retina.
- Field of view does not apply.
- Scans are defined in terms of scan length (mm).
- Pixelation and aspect ratio may vary among scans.
- No single scan can universally define a widefield OCT scan.
- The description should include:
  - scan size;
  - location;
  - scan type;
  - whether or not it is a montage; and
  - symmetry.

For OCTA scans, the key definitions are slightly different:

- *Widefield*—retina in all four quadrants and include the retina up to the posterior edge of vortex vein ampullae.
- *Ultra-widefield*—retina in all four quadrants beyond the anterior edge of the vortex vein ampullae.

Story behind International Widefield Imaging Study Group

The IWFISG involved 11 of the more senior thought leaders in the field who decided to get together to find a formal way to tackle the problem of trying to define the terms used to describe ophthalmic images. SriniVas R. Sadda, MD, of the University of California Lost Angeles Stein Eye Institute and I developed the format for the consensus proceedings. We selected the consensus panel participants based on their published work on retinal imaging.

Each member was sent the following set of seven individual, high-quality images from the most commonly used imaging modalities from both normal and diseased eyes:

- Swept-source optical coherence tomography montage image extending from the nasal to the temporal equator in an eye with a macular hole (DRI Triton, Topcon).
- A pseudocolor image extending from the nasal to temporal ora seratta in an eye with peripheral retinal holes (Optos Tx-200).
- A normal fundus photograph montage spanning a reported 110 degrees (Eidon, CenterVue).
- Fluorescein angiogram montage of an eye with Coat's disease (Optos Tx-200).
- Swept-source OCT B-scan through a vortex vein (DRI Triton, Topcon).
- Asymmetric panretinal OCT montage of senile retinoschsis (Heidelberg Spectralis).
- Swept-source 12 x 12 mm OCT angiography of a normal fundus (Plex-Elite, Carl Zeiss Meditec).

The package did not provide any device-specific information.

We asked the members to note what the images showed, what terms they would use to describe them and how they would define those terms. The pre-meeting preparation also included a review of the peer-reviewed published literature using the search terms widefield and ultra-widefield, and a systematic review of the numerous advances in obtaining progressively wider retinal images. Each member presented their findings to the group before the roundtable meeting.

At the meeting, the members discussed their findings from each of the seven test images with the goal to determine how we should best define the terms. The most frequently used term from the pre-meeting survey was used as the focus of the discussion. The dialog carried on until the group reached unanimous consent on a term.

— N.C.

Field of view

These definitions are predicated on the definition of *field of view*; that is, the macula should be at the center of the image, and the cut points should correspond to commonly visualized anatomical features—the vortex vein ampullae. The IWFISG also made recommendations for key regions within the retina (*Table, page 27*).

There are variations on these definitions:

- *Asymmetric widefield* or *ultra-widefield*—an image that captures only the temporal, nasal, superior or inferior aspects of the retina.
- *Montage*—a scenario where photographers take multiple images and stitch, or montage, them together to provide the full perspective, but this isn't really a single-capture image; this is, instead, *widefield montage*, indicating that it was put together by multiple images.

Some of this becomes academic but descriptive because in retinal imaging we describe findings. From the reader's or investigator's perspective, it creates a roadmap as to how a particular image was captured.

There are caveats. Montaging images involves image overlap, and sometimes data may be lost. But a single-capture image does not in theory lose data. The editing process to create a montage image may inadvertently leave out some details. So an image that's called simply a *widefield*

These definitions are predicated on the field of view; that is, the macula should be at the center of the image, and the cut points should correspond to commonly visualized anatomical features—the vortex vein ampullae.

photograph implies single-image capture.

OCT-specific definitions

In OCT applying the anatomical boundaries for *widefield* or *ultra-widefield* definitions can be difficult because OCT doesn't capture all four vortex veins in all four quadrants. So the IWFISG felt that the descriptions for OCTs should be based on the length of the scan—9, 16 or 23 mm—and then, again, also to indicate whether a montage was used, and whether it's a structural B-scan that shows only the anatomy, or a full B-scan that shows blood flow, such as that seen with OCT angiography

And then, the IWFISG felt the terminology must also address the region the scans capture. A scan of the macula that's part of the posterior pole would be a *9-mm, posterior pole, structural B-scan*. An image farther out in the periphery toward the pars plans would be a *3-mm, far peripheral, structural B-scan*. These descriptions tell the reader the region of the retina the scan is from, the length of the scan and whether the scan is showing structure or flow.

Describing images has become so complicated only because our technology is advancing rapidly and our modalities are expanding. We must be descriptive in how we communicate with each other. It's not that different from the way radiologists describe MRI and CT-scans. They're very descriptive of whether it's a diffusion-weighted image, whether dye has been used, where the cuts are, or whether it's a coronal scan or a sagittal scan.

Describing images has become so complicated only because our technology is advancing rapidly and our modalities are expanding. We must be descriptive in how we communicate with each other.

Are manufacturers on board?

The IWFISG has shared our consensus definitions with the manufactures of these devices. We purposefully included all the different manufacturers' images to eliminate bias in our findings. Ultimately, it's the physicians and the discipline of rational medicine that defines how we choose to describe these terms. Hopefully, industry will follow and respect the definitions that we're putting forward, and, at the same time, work internally to try to achieve that panretinal image. That's really the holy grail for all of us as practitioners. If we can capture all the data in one image, we can walk through our patient day quickly and provide the greatest amount of information.

What's next for IWFISG

The next action for the group is to continue to evaluate new technologies together and help position them in terms

The International Widefield Imaging Study Group members

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The group members have a number of disclosures that include all of the ophthalmic imaging device manufacturers.

Table. Definitions for key regions within the retina

Region	Field of view	Anatomical location
Posterior pole	~50 degrees	Retina just beyond the disc and arcades
Midperiphery	~60 to 120 degrees (widefield)	Retina up to the posterior edge of the vortex vein ampulla
Far periphery	~110 to 220 degrees (ultra-widefield)	Anterior edge of vortex vein ampulla and beyond to pars plana

of where they fit into our practice, how we would define them and what their strengths and limitations are. As new technology emerges and new machines come out, we will be able to provide feedback on where they're strong, where they need to be improved and where they're best utilized. We have many great devices from many great manufacturers, and each device has a unique niche and a unique position in the work that we do.

Bottom line

No two devices are alike. Each has a strength, whether it's an ability to capture an image quickly, the quality of the image, the software, the analytics, the speed of use, patient preference or comfort, they all vary in a variety of ways. Side-by-side comparisons of all devices are challenging, so the study group's recommendations for terminology are all the more important. RS

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Retina Rounds: Melanoma? Or pseudomelanoma?

(Continued from page 12)

can have hollow, intermediate, solid or irregular acoustic quality. Intravenous fluorescein angiography reveals patchy blockage of choroidal fluorescence related to subretinal hemorrhage, sub-RPE hemorrhage or RPE hyperplasia.[4]

Observation is appropriate for asymptomatic patients because most PEHCR lesions stabilize or regress with time. Vitrectomy may be indicated for visual impairment due to associated vitreous hemorrhage.

Potential role for anti-VEGF

There is no standard of care for patients who become symptomatic due to macular extension of subretinal hemorrhage or fluid. However, anti-VEGF treatment may have potential benefit. A series in Turkey involved 12 eyes with two or three consecutive intravitreal injections of bevacizumab.[7] In nine eyes (75 percent), the PEHCR lesions significantly regressed, while in three eyes (25 percent), the lesions extended into the macula despite treatment.

A German series treated nine eyes with an average of three anti-VEGF injections (either 1.25-mg bevacizumab or 0.5-mg ranibizumab [Lucentis, Genentech/Roche]) to achieve complete resolution of macular subretinal fluid.[8] In three eyes, subretinal fluid reappeared after an average of 10 months, and 2.5 anti-VEGF injections were necessary to attain complete resolution of macular subretinal fluid for a second time.

Cryotherapy, laser photocoagulation, photodynamic therapy and intravitreal steroid therapy have all been proposed as potential treatments for PEHCR. However, further investigations are needed to demonstrate the efficacy of these treatments. RS

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Retinal imaging and neurodegenerative disease

A review of retinal changes and potential biomarkers in Alzheimer's, Huntington's and Parkinson's diseases.


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Take-home points

- Because of the correlation between ocular pathology and neurodegenerative disease, ocular imaging is a potentially powerful tool in diagnosis and treatment trials.
- Studies of optical coherence tomography angiography have found reduced vascular density, foveal avascular zone enlargement and reduced flow rates in patients with Alzheimer's disease.
- Retinal imaging studies in Huntington's disease, though limited, have reported ocular pathology including reduced retinal nerve fiber and ganglion cell layer thickness.
- In Parkinson's disease, retinal volume loss and RNFL thickness that correlates with disease progression and visual function have been reported.

The retina and the central nervous system share embryologic origin, and it's thought that changes in retinal tissue may mirror those in the brain, especially in neurodegenerative disease states. Neurodegenerative disease is a general term that describes many nervous system disorders characterized by progressive death of neurons.

The idea that neurodegenerative diseases (ND) may have ocular manifestations was popularized in 1986 when researchers at the University of Southern California identified widespread degeneration of axons in the optic nerve in postmortem subjects with Alzheimer's disease.[1] This further promoted the notion that other neurodegenerative diseases may also have ocular manifestations.

NDs as a group are a common cause of morbidity in the older population and a major unmet medical need both in terms of diagnosis and treatment. Neurodegenerative diseases are typically associated with progressive change and decline in cognitive function, behavior, motor and other brain functions, eventually leading to dementia.[2] Today, 50 million people worldwide are living with dementia and, as life expectancy continues to rise, this number is expected to triple by 2050.[3]

Making the diagnosis of neurodegenerative diseases

The differential diagnosis of neurodegenerative disease represents a major clinical challenge with significant overlap of symptoms despite disparate pathologies. The gold standard for the definitive diagnosis is brain pathology obtained at autopsy. However, deep clinical phenotyping with *in vivo* investigations such as structural and molecular brain imaging and cerebrospinal fluid (CSF) analyses can provide a probabilistic diagnosis premortem, such as "possible" or "probable" Alzheimer's dis-

ease.[4] However, these methods are costly, invasive, time consuming and are rarely performed before the onset of irreversible clinical symptoms. Therefore, there is a dire need for cheap, non-invasive, practical and precise screening tests for evaluation of people at risk for dementia. Because of the noted correlation between ocular pathology and ND, imaging of the eye represents a potentially powerful avenue for augmenting their diagnosis and treatment.

Retinal imaging technology has advanced considerably in the past few decades. Non-invasive, highly precise, *in vivo* evaluation of retinal tissue represents a feasible and cost-effective method for developing biomarkers in both advanced and presymptomatic patients.[5] Here, we will review retinal changes and potential biomarkers identified via retinal imaging in some of the most common forms of neurodegenerative disease.

Alzheimer's disease

Alzheimer's Disease, the most prevalent subtype of neurodegenerative disease, affects 5.8 million people in the United States alone and is the sixth leading cause of death. While the exact pathogenesis is not clear, AD is characterized by aggregation of abnormal extracellular beta-amyloid (Aß) plaques and intracellular tau neurofibrillary tangles, which may precede symptom onset by decades. However, histological and *in-vivo* retinal imaging studies have revealed multiple manifestations of the disease in the retina itself. Perhaps most intriguing is the recent identification of Aß and tau deposition in postmortem retinal tissue, which appears to follow a perivascular pattern.[6]

In support of this pathological evidence, numerous retinal changes in AD have been reported *in vivo*. Mild cognitive impairment (MCI) is a term used to describe the first identifiable symptoms of dementia.

Even in this early disease state, both significant atrophy and hypertrophy of the retinal nerve fiber layer have been reported when comparing MCI patients to healthy controls.[7] Increased RNFL thickness may indicate a later-MCI/early-AD process, since inflammation may cause local thickening prior to tissue loss, but the bulk of evidence suggests that subtle retinal changes occur in even the earliest stages of disease. In advanced stages, findings are more or less unanimous, indicating significant neurodegenerative processes such as thinning of the RNFL and ganglion cell layer (GCL), and loss of dendritic arborization when comparing AD patients to controls.[6]

Neurovascular changes in AD

Recently, researchers have turned their attention toward neurovascular changes in AD. Here, the retina provides a unique opportunity to quantify CNS microvasculature *in vivo* with a resolution not available elsewhere. Studies examining retinal vasculature alteration in AD can be categorized by either the structure or function of retinal vessels. Likely due to low measurement sensitivity, studies extracting vascular measures from fundus imaging have reported conflicting findings when comparing venular and arteriolar caliber, tortuosity and fractal dimension between AD and controls.[8,9]

However, there seems to be a trend toward reduced vascular function when comparing AD to controls, with increased arteriolar and venular oxygen saturation, reduced blood flow and speed, and exaggerated and prolonged neurovascular coupling.[10-12] Recently, optical coherence tomography angiography has become a preferred measurement of retinal vasculature, with improved resolution and sensitivity over other imaging modalities.[13] Studies using OCTA have reported reduced vascular density, enlargement of the foveal avascular zone and reduced flow rates when comparing AD patients to controls.[14,15]

Huntington's disease

Huntington's disease or Huntington's chorea is a heritable, fully penetrant and fatal ND characterized by cognitive, motor and psychiatric disturbance due to

Bios

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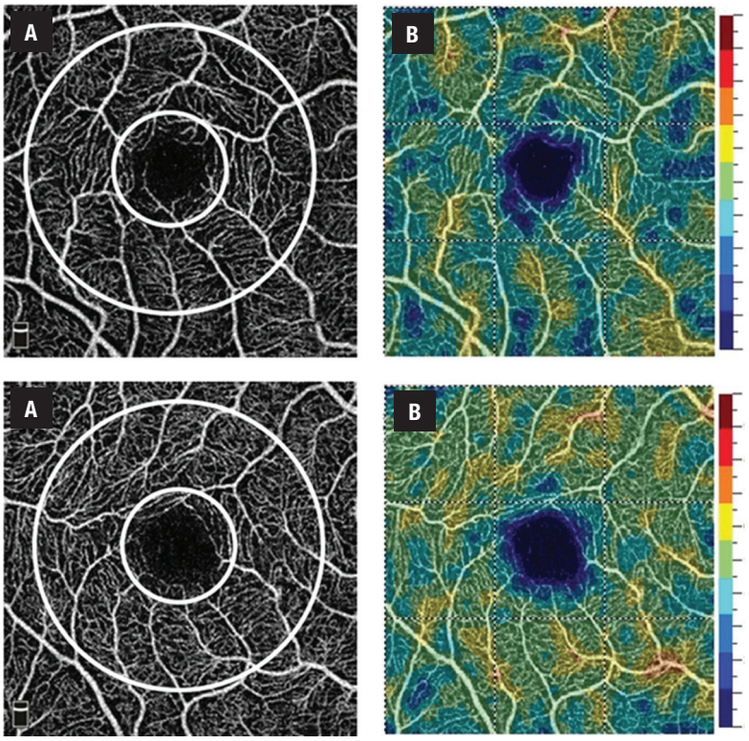

The superficial retinal optical coherence tomography angiograms of the macula (A) and color-coded vessel density maps (B) in a healthy control and in a patient with Alzheimer's disease. The foveal flow density (diameter of 1 mm, small white circle), parafoveal flow density (diameter 1 mm to 2.5 mm) and flow density whole en face (the average flow density of the entire 2.5-mm circle) were analyzed. (Used with permission of IOS Press. J Alzheimer's Dis. 2018;66:1745–1752)

atrophy of the basal ganglia and cerebral cortex. In western populations, its prevalence is 10.6 to 13.7 per 100,000. Unlike most neurodegenerative diseases, the pathology and cause of HD are relatively well understood—an autosomal dominant mutation in the huntingtin (HTT) gene.[16] Visual dysfunction and perceptual disturbance in HD are well documented and have been reviewed thoroughly elsewhere.[17]

However, retinal imaging studies in HD are limited. To the best of our knowledge, only four groups have reported on them over the last decade. These studies found reduced temporal pRNFL thickness; reduced macular RNFL, GCL, inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) and choroidal thickness; and no significant difference between total macular volume and global pRNFL between HD patients and controls.[18-21]

In addition, pRNFL and macular thicknesses were found to negatively correlate with disease duration and the Unified HD Scale Motor Score in HD patients.[18,20,21]

Parkinson's disease

Parkinson's disease is one of the more common neurodegenerative diseases in the developed world, with a prevalence of 0.3 percent and an estimated incidence of eight to 18 out of 100,000.[22] Disability in PD is thought to result from dysregulation and degeneration of dopaminergic neurons in the basal ganglia, accompanied by reduction of the catecholamine neurotransmitter dopamine.[23] PD is a multi-system disorder characterized by both motor symptoms, such as tremor, bradykinesia and rigidity, as well as cognitive decline, hyposmia, autonomic failure and visual disturbance.[22]

Visual disturbance in PD ranges from reduced visual acuity to complex hallucinations, symptoms that are not confined to the retina, involving posterior cortical regions.[22] However, several reports have demonstrated significant changes in retinal structure in PD. Reduced peripapillary RNFL thickness has been found globally in PD patients compared to controls.[24] Reduced total macular thickness has also been observed in PD patients with more significant thinning demonstrated in the inner retinal layers.[24] In addition to observed group differences in retinal volume loss, RNFL thickness has been reported to correlate with disease progression, as well as visual function.[24]

Researchers in Spain were able to confirm these findings longitudinally, reporting higher rates of RNFL thinning and reduction in macular thickness at five-year

follow-up.[25] Researchers in South Korea found that macular thickness was significantly correlated with dopamine transporter uptake density in the *substantia nigra*, indicating that retinal thinning was associated with dopaminergic neuronal loss in the basal ganglia.[26]

Emerging imaging modalities

While OCT has been the mainstay for identifying many retinal changes found in neurodegenerative diseases, a number of emerging technologies hold additional promise. In addition to OCTA, three additional technologies are at much earlier stages of investigation, but have already begun to yield insights into AD.

• ***Fundus autofluorescence.*** This imaging method is designed to capture the intrinsically fluorescent features of retinal tissue. For example, as RPE cells phagocytize outer segments, lipofuscin accumulates in the cells. Lipofuscin can fluoresce when stimulated by light from a broad spectral range spanning from 500 to 800 nm. Excess lipofuscin accumulation in surviving RPE will appear as hyper-autofluorescence, whereas RPE atrophy and loss will result in hypo-autofluorescence. Other retinal features may also have autofluorescence patterns that are in the early stages of research. For example, beta amyloid accumulation may also be associated with autofluorescence that has yet to be clearly described.

• ***Fluorescence lifetime imaging ophthalmoscopy.*** FLIO is a new autofluorescence-based system that utilizes the FAF signal but measures the FAF signal duration or lifetime. The concept of measuring fluorescence lifetime decay in theory should provide more sensitivity and specificity for detecting pathological changes. FLIO has been used to describe early changes in macular telangiectasia type 2 (MacTel) and age-related macular degeneration as well as other degenerative diseases, which may impact macular pigments.[27-30]

• ***Dynamic vessel analysis.*** DVA is a system that evaluates real-time morphological changes in the retinal microvasculature in response to stimuli presented in the form of flickering lights. Eyes of healthy controls have been shown to demonstrate a characteristic response curve, with primary vasodilation and secondary vasoconstriction when presented with the stimulus. AD patients have been shown to not only have a decreased reaction amplitude but a reduction in arterial dilation as well.[31] This change has been described as a downstream effect of neurovascular decoupling in the progression of both vessel and nerve disease.

Limitations of imaging studies

As with any emerging field, there are several limitations to the conclusions gleaned from these imaging studies. First and foremost, there is no direct causation yet established between Alzheimer's disease severity, duration or progression with RNFL thickness or microvascular density. This is related to the question of receiving an AD diagnosis in and of itself and the fact that the site of disease—the brain—is rather inaccessible until postmortem in most cases.

Moreover, diseases such as AMD, glaucoma, vascular diseases including diabetes and hypertension, and other confounders that affect the macula are prevalent in aging populations and may be overestimating the contribution of AD to these measurements.

The impact of medications used to treat these diseases themselves can have effects on the measurements of microvascular morphology, further confounding conclusions. Ultimately, longitudinal studies using well-developed and established imaging modalities will need to be conducted to tease apart the multifactorial contributions to retinal changes that have been identified in neurodegenerative disease.

Bottom line

An ounce of prevention is worth a pound of cure. By monitoring thinning in the GCL and RNFL, watching for changes to vessel morphology and assaying vessel density, we

Three imaging technologies in addition to OCTA that hold promise for identifying retinal changes found in neurodegenerative disease are at earlier stages of investigation.

may be able to combine different imaging modalities to determine a patient's diagnostic likelihood for dementia. We may then begin to answer questions regarding prevention and treatment efficacies and make observations on whether retinal changes are progressive, and whether they can be reversed. In this way, noninvasive ophthalmic imaging is likely to continue to develop an increasing role in the diagnosis and possibly management of subjects with dementia.

By monitoring the GCL and RNFL, watching for vascular morphology changes and assaying vessel density, we may be able to combine different modalities to determine a patient's prognosis for dementia.

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The potential of retinal imaging in predicting neurodegenerative disease

As the burden of dementia and mild cognitive impairment grows in the next several decades, so too does the need for better diagnostic and treatment modalities. Several retinal imaging technologies stand to make major contributions to the evaluation and potentially even the management of one or more causes of dementia. A precedent for this has already been set through the use of optical coherence tomography in the evaluation of subjects with multiple sclerosis and other neurodegenerative diseases described above.

The relatively easy accessibility of the retina compared to the intracranial central nervous system tissue provides a unique opportunity to directly visualize pathologic changes with unprecedented resolution. This may allow researchers as well as clinicians to develop new insights into the disease pathogenesis as well as develop novel therapies. RS

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IOP and anti-VEGF drugs: What we know so far

Chronic changes in intraocular pressure may be dependent on the anti-VEGF drug used. A look at emerging research on physiology and the role of genetics.

By Lauren Burgett and Raj K. Maturi, MD

Take-home points

- Immediately following an injection of ranibizumab, nearly 90 percent of eyes have been reported to have an intraocular pressure of > 30 mmHg.
- A recent analysis of the IRIS registry found a small and probably not clinically significant decrease in IOP from anti-VEGF injections over time, but a small percentage of patients had an IOP increase that could be clinically significant.
- Research has suggested that the rise in IOP may be related to anti-VEGF interaction with nitric oxide physiology and/or three polymorphisms of the CD36 gene.
- Further clinical studies are needed to better understand the mechanism responsible for chronic IOP increases after anti-VEGF injections.

Acute intraocular pressure increases are a well-known common complication of intravitreal anti-VEGF injections. A study in Italy found that 88.9 percent of eyes had an IOP of greater than 30 mmHg directly following injection of ranibizumab (Lucentis, Genentech/Roche).[1] A study conducted by Judy Kim, MD, and colleagues at the Medical College of Wisconsin found that IOP rises to a mean of 44 mmHg immediately after intravitreal injection, then quickly declines to below 30 mmHg within 15 minutes.[2] In both of these studies, IOP approached normal levels 30 to 60 minutes post-injection for a majority of patients.

Chronic IOP change

A recent analysis using the IRIS registry has found a small but statistically significant decrease in IOP with use of anti-VEGF injections. Conducted by Elizabeth Atchison, MD, and colleagues, the study analyzed 23,776 unique patients from the IRIS registry who had been diagnosed with neovascular age-related macular degeneration, diabetic macular edema, branch retinal vein occlusion or central retinal vein occlusion.[3] Patients received injections of bevacizumab (Avastin, Genentech/Roche, 56 percent), ranibizumab (25 percent) or aflibercept (Eylea, Regeneron Pharmaceuticals, 19 percent) in the right eye but no treatment in the left. Only patients with at least 12 injections of the specified anti-VEGF were examined.

All subgroups of patients showed a small mean decrease in IOP from the baseline to the last injection. On average, the bevacizumab patients had a 1.2-mmHg decrease in IOP in the treated eye compared to aflibercept with a 0.5-mmHg


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

Ms. Burgett has no financial disclosures.

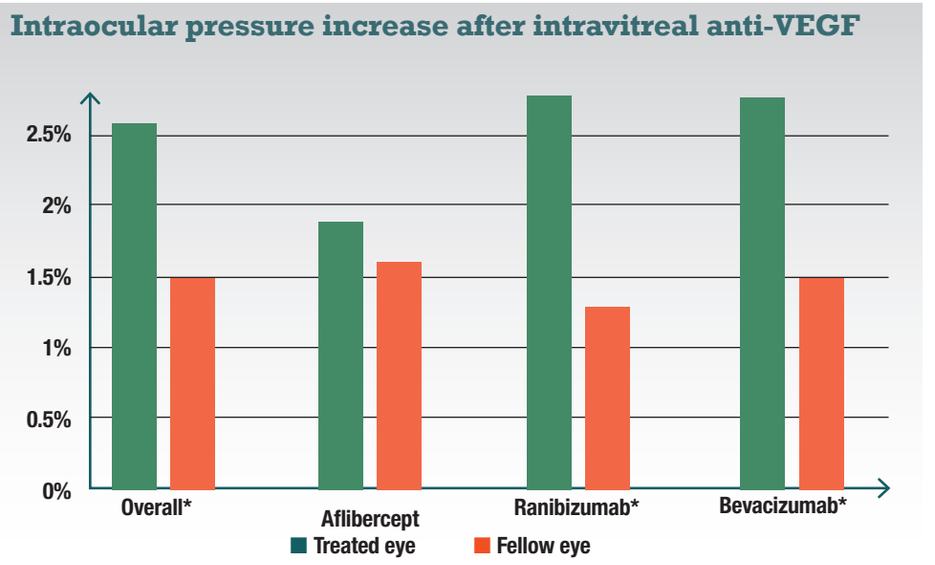

Figure. This graph shows the percentage of patients receiving ≥12 intravitreal anti-VEGF injections with a statistically significant intraocular pressure rise in the treated eye in comparison to the fellow untreated eye (*indicates statistically significant difference between treated and fellow eye). (Adapted from Atchison EA, Wood KM, Mattoz CG, et al. The real-world effect of intravitreous anti-vascular endothelial growth factor drugs on intraocular pressure. Ophthalmology. 2018;125:676-682.).

Decreased IOP after anti-VEGF injections is small and likely not of clinical importance, but the small percentage of patients that experience an increase in IOP could be of clinical significance.

decrease. The change for patients on ranibizumab was lower—a 0.2-mmHg decrease. Average fellow-eye change in IOP for all groups was a 0.2-mmHg decrease. While these changes are all statistically significant, the small mean decrease may not be of significant clinical importance.

On the other hand, incidents of clinically significant IOP rises, defined by the researchers as an increase of ≥6 mmHg from baseline resulting in an IOP ≥21 mmHg for were 2.6 percent overall vs. 1.5 percent in the fellow eye (*Figure*). The difference in IOP between treated and untreated fellow eyes was statistically significant for bevacizumab and ranibizumab, but not aflibercept. However, it's important to note these numbers don't account for the use of IOP-lowering medications, such as glaucoma drops.

Concern about increased IOP

While this study lacks the structure of prospective clinical trials, its use of real-world data reflects current clinical practice. The finding of decreased IOP from anti-VEGF injections, while proven statistically significant, is small and likely not of clinical importance. However, the small percentage of patients that experience an increase in IOP could be of clinical significance.

Currently, the exact mechanism that causes this adverse reaction is still under investigation. Additionally, the finding that aflibercept didn't create any significant increase in IOP in a subgroup of patients compared to bevacizumab and ranibizumab requires further study. For example, could the authors now choose the left eye as the primary eye and run the same statistics to see if the same outcome could be achieved?

How anti-VEGF may influence IOP

Important differences between bevacizumab, ranibizumab and aflibercept lie in their pharmacodynamics, mechanisms

of action and targets. All three drugs are antagonists that bind to the active site of human vascular endothelial growth factor A inhibiting the ligands (VEGFR-1 and VEGFR-2) from binding to their endothelial receptors. Aflibercept has the highest binding affinity of the currently used anti-VEGF drugs.

While ranibizumab and bevacizumab only target VEGF-A, aflibercept targets placenta growth factor and VEGF-B as well.[4-6] The half-life of aflibercept is estimated to be six days vs. nine days for ranibizumab and bevacizumab.[7] All of these chemical differences could be contributing factors as to why aflibercept does not exhibit the same rate of chronic IOP rise.

Nitric oxide pathway

Aaron Ricca, MD, and colleagues at the University of Arkansas, suggested a physiologic vascular hypothesis for IOP increase arises from alteration of the nitric oxide pathway,[8] which is known to relax smooth muscle and endothelial cells. Components of the nitric-oxide pathway have been identified in the anterior chamber. Nitric oxide has been shown to increase anterior chamber aqueous outflow by decreasing trabeculocyte size and vasodilating Schlemm's canal.

Through its oncologic applications, anti-VEGF is known to disrupt the normal nitric oxide signaling pathway. When used systemically, anti-VEGF therapy is known to increase arterial hypertension through this mechanism. Taken together, this suggests that increases in IOP may be related to anti-VEGF interaction with nitric oxide physiology.

Genetics and IOP

A potential genetic basis for increased IOP after anti-VEGF therapy has been identified. Researchers in Australia and Europe examined 134 patients that received ranibizumab and identified three polymorphisms of the *CD36* gene that were associated with significant IOP increase after therapeutic injection.[9] One of the polymorphisms, rs1049673, was associated with pronounced IOP rise (IOP > 25 mmHg).

More connections between genetic and physiological factors are emerging. A National Institutes of Health study has demonstrated thrombospondin-1 inhibition of nitric oxide signaling via CD36.[10] Richard Morshedi, MD, and colleagues proposed a clearer mechanism: Anti-VEGF upregulates nitric oxide synthase, decreasing nitric oxide in the anterior chamber and creating decreased trabecular meshwork outflow, thereby increasing IOP.[11]

Bottom line

Further clinical studies need to be carried out to better understand the complete mechanism responsible for chronic IOP increases as a complication of anti-VEGF injections.

Increases in IOP may be related to anti-VEGF interaction with nitric oxide physiology.

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Report from AAO Retina 2019 Subspecialty Day

First results of gene and cell therapies for nAMD, RP, plus ...

Findings on predictors of endophthalmitis, widefield OCT-A vs. FA and microsecond pulsing laser make five worthy takeaways.

Ashkan M. Abbey, MD

By Ashkan M. Abbey, MD

Take-home points

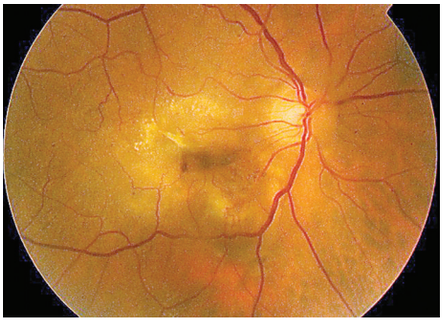
- Intravitreal gene therapy shows promise for one-time treatment of neovascular age-related macular degeneration.
- Cell therapy demonstrates signal for treatment of retinitis pigmentosa.
- A multivariate analysis identified two independent predictors of endophthalmitis after intravitreal anti-VEGF injections.
- Microsecond pulsing laser proves potential for treating chronic central serous chorioretinopathy.
- Widefield optical coherence tomography and ultra-widefield fluorescein angiography demonstrate roles for evaluating nonperfusion.

As the last major ophthalmology conference of the year, the American Academy of Ophthalmology seems to host an inordinate share of pivotal clinical trial readouts in all fields of ophthalmology, but especially in retina. At the Retina 2019 Subspecialty Day, which actually takes up two full days, no fewer than 14 presentations were of late-breaking developments or first-time results of clinical trials. Here, we share summaries of five compelling study readouts from AAO.

First results of intravitreal gene therapy for nAMD

The Phase I OPTIC trial evaluated an intravitreal gene therapy, ADVM-022 (Adverum Biotechnologies), for the treatment of neovascular age-related macular degeneration. ADVM-022 uses a proprietary vector capsid, AAV.7m8, to carry an aflibercept expression cassette.[1] It's a one-time injection designed to increase transduction of retina cells and increase expression of the anti-VEGF protein.

Szilard Kiss, MD, of Weill Cornell Medical College in New York, reported on 24-week data from the first cohort dosed in OPTIC (n=6). Patients received an injection of aflibercept at baseline before the ADVM-022 injection. The cohort reported no serious adverse events.



A proprietary vector capsid carries an aflibercept expression cassette to target neovascular age-related macular degeneration. {National Eye Institute photo)

Bio
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.

Of the 19 adverse events potentially related to ADVM-022, 14 were mild in nature while five were moderate. No early clinically significant inflammation, vasculitis, retinitis or choroiditis occurred, and use of steroid drops did not worsen symptoms. Any anterior chamber cellular inflammation improved by week 24.

The trial is enrolling three other cohorts, and 52-week data on the first cohort is due in the first half of 2020. The company is also preparing an investigational new drug application in diabetic retinopathy in the same time frame.

The take home: Average change in BCVA was a loss of 2 letters at 24 weeks, and central subfield thickness decreased 52.7 µm. No patients required a rescue injection over 24 weeks. Updated results out to 34 weeks reported no additional adverse events and an improvement in BCVA to a loss of 1.5 letters.

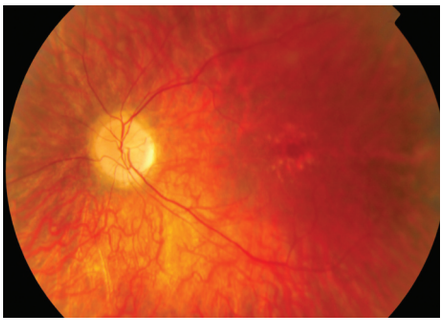
Dr. Kiss is a consultant and adviser to Adverum, RegenxBio and Fortress Bio, and holds equity in the companies. He is also a consultant and adviser to Genentech/Roche and Novartis.

First-time results of cell therapy for RP

A cell therapy treatment for retinitis pigmentosa is the focus of a Phase I/IIa trial that Pravin U. Dugel, MD, of Retinal Consultants of Arizona, Phoenix, reported on. The subretinal human retinal progenitor cell (hRPC) is the subject of a Phase I/IIa trial. The therapy uses cells isolated from fetal retinas. It can differentiate into retinal cells and can be cryopreserved with a shelf life of nine months. The therapy does not require immunosuppression.

Among the potential benefits of hRPC are the ability to deliver it directly into the subretinal space, on-demand shipment to the clinic and its ability to treat any genetic subtype of disease.

The Phase I trial treated 12 patients with doses of 250,000 or 500,000 fresh cells or 1 million cryopreserved cells. Because of the good safety profile, the Phase IIa trial consisted of 10 patients receiving a 1-million-cell dose.[2]



First readout of a trial of cell therapy for retinitis pigmentosa shows safety and confirms a biological signal. {NEI photo)

The first 22 patients tolerated dose escalation well and had no inflammation or proliferative vitreoretinopathy. There were two serious adverse ocular events unrelated to the drug. Two events leading to vision loss were related to the operation itself or patient selection: a retinal pigment epithelium tear; and persistent subretinal fluid. At 38 weeks post-treatment, BCVA improved an average of 12 letters in the treated eye vs. a 1-letter loss in the untreated eye.

The take home: The trial confirms a biological signal, although the speed of the effect varies among patients. The study results should help improve patient selection and surgical procedure standardization for future trials.

Dr. Dugel disclosed he is a consultant to ReNeuron PLC, the trial's sponsor.

Predictors of endophthalmitis and IVT anti-VEGF injections

Complications of intravitreal anti-VEGF injections, while infrequent, are confounding and concerning for anyone who does a fair volume of procedures. Tarek Hassan, MD, reported on a retrospective analysis of 154,198 anti-VEGF injections by 15 retina specialists over three years at his practice, Associated Retinal Consultants in Royal Oak, Michigan.[3] The goal was to identify predictive factors

Among the potential benefits of human retinal progenitor cells are delivery directly into the subretinal space, on-demand shipment to the clinic and its ability to treat any genetic subtype of disease.

for endophthalmitis after IVT, evaluating each provider's protocol. The preinjection protocol the providers followed consisted of povidone iodine (PVI) before and after anesthesia, typically subconjunctival or topical lidocaine.

Fifty-eight cases resulted in endophthalmitis, an incidence of 1:2,659, 41 percent culture positive. Multivariable analysis excluded same-day bilateral injections and cases by physicians with inconsistent injection protocols, resulting in 98,960 unilateral injections. Of those, 40 cases resulted in endophthalmitis, an incidence of 1:2,474, 42.5 percent culture positive.

The take home: The multivariate analysis identified two independent predictors of endophthalmitis: preinjection use of 1% lidocaine jelly, with an 11 times greater odds of endophthalmitis ($p<0.001$); and preinjection use of 0.5% tetracaine with a fourfold risk ($p=0.03$). The study also noted that *in vitro* studies have shown an increased risk of microbial survival in the eye when lidocaine gel is used before the application of PVI,[4,5] which may explain this study's results. The analysis also determined that the use of 5% vs. 10% PVI tended to not improve or worsen endophthalmitis. Study results were published previously in *Ophthalmology Retina*.[6]

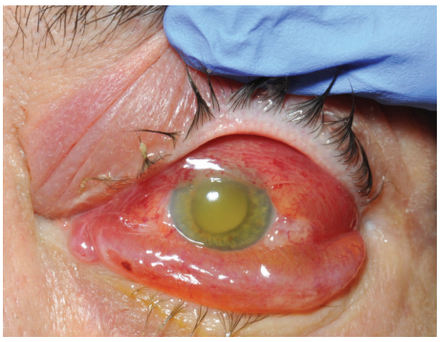
Dr. Hassan disclosed relationships with Alcon, Allergan, Genentech/Roche, Novartis and Regeneron Pharmaceuticals.

Multivariate analysis identified two independent predictors of endophthalmitis: preinjection use of 1% lidocaine jelly; and preinjection use of 0.5% tetracaine.

Microsecond pulsing laser vs. PDT in CSCR

A study involving patients with chronic central serous chorioretinopathy compared the effectiveness of microsecond pulsing (MSP) laser and photodynamic therapy, giving an edge to the former because of its less-invasive nature and improved patient comfort and cooperation.[7]

Jay Chhablani, MD, of the University of Pittsburgh reported on five studies comparing the two modalities, noting that outcomes were superior with MSP laser than half-fluence or half-dose PDT, but that the differences in improvements between the two groups were not significant. However, in one of the five surveyed studies, the study group reported a statistically significant visual acuity outcome with MSP laser.[8]



The timing and choice of anesthesics and povidine iodine before intravitreal injections may be related to the risk of endophthalmitis. {NEI photo)

The take home: Choroidal neovascularization is a side effect of PDT while MSP laser didn't show any side effects. Further, while the conventional MSP laser and navigated laser (Navalis) are "laser equivalent," this study showed the navigated platform required significantly lower fluence with significantly fewer laser impacts than PDT, resulting in a higher rate of complete resolution with a statistically better best-corrected visual acuity. This effect may be attributed to the navigation. Additionally, the navigated platform can be used without a contact lens, "definitely improving the patient comfort and cooperation," Dr. Chhablani said.

Dr. Chhablani has no disclosures.

WF OCT-A surpasses FA for evaluating nonperfusion

Anti-VEGF therapy for diabetic macular edema has been known to improve the diabetic retinopathy severity scale (DRSS) score when evaluated with color retinal photography and stanch the progression of DR, but the role of anti-VEGF therapy in retinal perfusion, as imaged with fluorescein angiography, remains a matter of conjecture.

(Continued on page 40)

Coding for surgery in the postop period

How to use modifiers 58, 78 and 79 for a planned or unplanned trip back to the OR.

Some surgical care doesn't end in a single operation, and the patient needs additional surgery in the postoperative period. Complex cases may be staged. Other cases may require an unexpected return to the operating room, or the patient may have bilateral disease. Here, I'll explore the correct documentation and coding for these situations.

New procedure

Modifier 58 is an important tool to allow a surgeon to bill for procedures when the patient requires a subsequent procedure following surgery. The definition of modifier 58 is:

Staged or related procedure or service by the same physician or other qualified health care professional during the postoperative period. It may be necessary to indicate that the performance of a procedure or service during the postoperative period was: (a) planned or anticipated (staged); (b) more extensive than the original procedure; or (c) for therapy following a surgical procedure.[1]

Some relatively common examples of when to use the 58 modifier include:

- preoperatively planned intravitreal anti-VEG-F injections after a pars plana vitrectomy for diabetic retinopathy (staged);
- preoperatively planned silicone oil removal after retinal detachment surgery with silicone oil (staged); and
- laser retinopexy for retinal hole followed by unanticipated retinal detachment and return to the operating room for vitrectomy and retinal detachment repair (more extensive than original procedure).

The term *staged* implies preoperative planning; the preoperative note for the first procedure should indicate the intention to perform a second procedure.

Modifier 58 can be used for procedures performed in the clinic or in the operating room. Payment for the second procedure isn't reduced; the postoperative clock restarts with the second procedure.

Unplanned return to OR

Modifier 78 is defined as, "Unplanned return to the operating/procedure room by the same physician or other qualified healthcare professional following initial procedure for a related procedure during the postoperative period."[2] The first thing you may notice is "return to the operating room." This is an important difference from modifier 58. Also, there is no preplanning or requirement that the second procedure be "more extensive."

Modifier 78 examples include:

- after epiretinal membrane peel, a return to the OR for vitrectomy for persistent vitreous hemorrhage; and
- after complex retinal detachment repair, a return to the operating room for vitrectomy and intravitreal antibiotics.

Note that an "operating/procedure room" does not include a physician's clinic-based procedure room. The Medicare Claims Processing Manual details what constitutes an OR: "An OR for this purpose is defined as a place of service specifically equipped and staffed for the sole purpose of performing procedures."[3] A dedicated laser suite may qualify as a procedure room.

Also note that if the second procedure is more extensive than the first, modifier 58 would apply. Modifier 78 reduces reimbursement and the postoperative clock is not reset; the postop period is calculated from the first procedure.

An unrelated procedure

Modifier 79 is significantly easier to understand than 58 and 78: "An unrelated

By Ellen R. Adams, MBA

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

Bio

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procedure or service by the same physician or other qualified healthcare professional during the postoperative period."[4]

Unrelated procedures may include:

- panretinal photocoagulation on one eye with PRP on the fellow eye within the global period of the first procedure;
- epiretinal membrane peel during a cataract postoperative period; and
- intravitreal anti-VEGF injection in the postoperative period of a vitrectomy on the fellow eye.

Note that the place of service isn't specified; an operating room or clinic service is allowed. The reimbursement for the second procedure is at 100 percent, and the postop periods for the first and second procedure run concurrently.

Documenting the preoperative plan accurately is important. The rationale for using 58, 78 or 79 hinges on the preoperative note. Having a full understanding of these important modifiers will allow you to submit accurate claims and assure appropriate documentation to support a second surgery in the global period.

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Report from AAO 2019

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Investigators in France and Italy speculated that the variation in the ability to evaluate the role anti-VEGF has in peripheral retinal perfusion may be related to the inability to delineate areas of nonperfusion even with ultra-widefield FA. The researchers conducted a small study to evaluate the correlation between the number of DR lesions on ultra-widefield fundus photographs and nonproliferation on UWF FA.[9]

The study compared UWF color photography and UWF FA at baseline and one month after three monthly anti-VEGF injections in 18 eyes of 14 treatment-naïve patients. In results previously published in *Retina*, they reported no reperfusion of the arterioles or venules in or near the nonperfusion areas when the DRSS score improved at least one stage in 11 eyes (61 percent, $p<0.0001$).[10] After three anti-VEGF injections, FA did not identify reperfusion of vessels despite DRSS improvement on color photographs.

Then the researchers used widefield optical coherence tomography angiography to evaluate DRSS, finding it improved at least one stage within three months after three monthly anti-VEGF injections or earlier in eight of 10 eyes, and that new vessels regressed. However, OCTA proved with better precision that no reperfusion occurred, even at the capillary level. These results are pending publication in *Ophthalmology*.[11] All nonperfusion areas detected on WF-FA were also detected on WF OCTA, and WF OCTA additionally detected some extra areas of nonperfusion that UWF-FA did not.

The take home: DRSS decorrelates from perfusion status after intravitreal anti-VEGF injections, and OCTA is superior to FA for evaluating nonperfusion. On UWF-FA, apparent changes in brightness of the background in areas of nonperfusion could lead to a misdiagnosis of reperfusion when WF OCTA finds no reperfusion. While WF OCTA can image an area larger than the seven standard field 30-degree color fundus photographs, UWF-FA may still be useful for areas WF OCTA can't reach.

Presenter Ramin Tadayoni, MD, PhD, disclosed relationships with Alcon, Allergan, Carl Zeiss Meditec and Genentech/Roche.

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Potential of KSI-301 to extend treatment

The latest results reported efficacy up to five months after the last loading dose.

Recently reported results of the Phase Ib trial of the investigational anti-VEGF agent KSI-301 (Kodiak Sciences) revealed promising data on the safety, efficacy and durability of the drug in patients with previously untreated exudative retinal diseases. Charles C. Wykoff, MD, PhD, reported the first results from the trial last month at Retina 2019 Subspecialty Day at the American Academy of Ophthalmology.[1]

KSI-301 is an intravitreal agent based on a novel platform, called antibody biopolymer conjugate, or ABC, that uses a large molecular structure to bind to and inhibit vascular endothelial growth factor.

In a press release reporting the latest Phase Ib results, Kodiak Sciences chief medical officer Victor Perlroth, MD, said the Phase Ib results support the company's intent to develop KSI-301 to reduce the treatment burden of existing anti-VEGF treatments while improving visual acuity. The findings have enabled Kodiak Sciences to begin enrolling patients in a global, multicenter, randomized Phase II trial called DAZZLE. This trial will eventually enroll at least 368 patients and compare KSI-301 on an individualized dosing regimen of three to five months and aflibercept (Eylea, Regeneron Pharmaceuticals) every eight weeks.

Here, Dr. Wykoff answers questions about the Phase Ib and Phase II trials. Dr. Wykoff, who is also chief clinical editor of *Retina Specialist Magazine*, is a paid consultant and researcher for Kodiak Sciences.

Q What makes KSI-301 different from other anti-VEGF agents that are available?

A Mechanistically, KSI-301 binds to VEGF-A as the other primary anti-VEGF agents. What makes KSI-301 unique is the projected durability of this effect inside of the eye. The antibody biopolymer conjugate platform on which KS-301 is based has been engineered specifically for increased durability. It has two components, a specific anti-VEGF IgG1 antibody with an inert immune effector function that is covalently and stably linked to an intentionally high molecular weight, optically clear phosphorycholine biopolymer.

The concept is to maximize intraocular durability by leveraging size and molar dose. The molecular weight of KSI-301 is 950 kilodaltons vs. 48 kDa for ranibizumab (Lucentis, Roche/Genentech) and 115 kDa for aflibercept. This, combined with a 3.5-fold greater molar dose than aflibercept, leads to an estimated intraocular anti-VEGF effect at three months that has been calculated, based on preclinical studies, to be 1,000-fold greater than aflibercept.

Q What did the preclinical studies reveal about the potential efficacy of KSI-301?

A Preclinical studies have demonstrated three key effects. First, in rabbit models the drug appeared to have a substantial durability benefit compared to previous generation anti-VEGF agents, with an estimated half-life in the rabbit retina to choroid of approximately 10 to 15 days. Second, it demonstrated excellent bioavailability at the target tissues—the retina and choroid. Third, because of its inert Fc domain, when the molecule does diffuse from the eye into systemic circulation, the anticipated primary route of exit from the eye, it clears from systemic circulation rapidly with a systemic half-life of less than one day, much less than bevacizumab (Avastin, Roche/Genentech, 11.5 days).

Q What were the key findings of the Phase Ia trial previously reported.

A That Phase Ia trial involved nine

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Combined with a 3.5-fold greater molar dose compared to aflibercept leads to KSI-301 having an estimated intraocular anti-VEGF effect at three months that has been calculated to be 1,000-fold greater than aflibercept.

patients with diabetic macular edema. They received a single dose of KSI-301, which showed a durability of effect through 12 weeks without any drug-related adverse events.

Q What was the design of the Phase Ib trial?

A The Phase Ib trial involved 105 patients—35 each with wet age-related macular degeneration, DME and retinal venous occlusive disease. These patients were randomized to 2.5- or 5-mg doses of KSI-301. All patients were given three monthly loading doses and then evaluated monthly, receiving retreatment when prespecified anatomic and/or visual criteria were met.

Q What are the key findings of the Phase Ib trial that you reported at the AAO?

A This is an ongoing study and the data I presented on behalf of my co-investigators were interim results. In the nAMD group, at 16 weeks, best-corrected visual acuity has improved 5.4 letters on average, and central subfield thickness decreased 72 µm on average. Eighty percent of these patients were able to be extended four months or longer before needing their first retreatment after the three loading doses. Among the DME population, BCVA improved an average of 8.4 lines at 16 weeks and CST improved 140 µm on average. Again a majority, or 82 percent, have so far been able to be extended longer than three months after the last loading dose, and some have been extended to six months before meeting retreatment criteria. Furthermore, all DME patients had either improved or maintained their diabetic retinopathy severity level and none developed a proliferative DR event.

In RVO, BCVA improved 21.3 letters on average at 16 weeks and CST decreased 353 µm (the baseline average CST was approximately 250 µm greater in this group than in the nAMD and DME groups). Among the RVO patients, 56 percent have so far been able to be extended beyond three months after their last loading dose.

Equally important to efficacy and durability, the safety profile of KSI-301 appears excellent, with no intraocular inflammatory events and no drug-related adverse events in 316 total treatments across the Phase I program thus far.

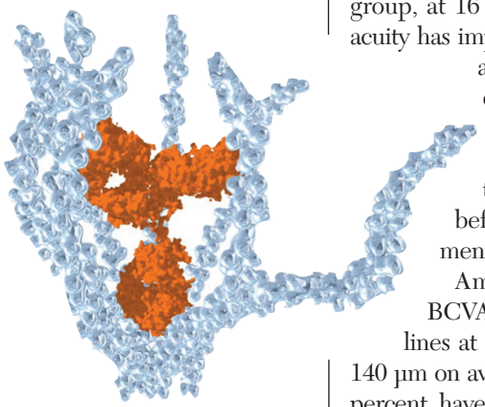
Q What are the next steps for KSI-301?

A The pivotal Phase II DAZZLE study is enrolling treatment-naïve nAMD patients and randomizing them to either 5-mg KSI-301 or aflibercept. KSI-301 is being dosed every 12, 16 or 20-weeks depending on prespecified disease activity assessments and the primary endpoint is at one year.

Q Where would KSI-301 potentially fit in the retina specialist's toolbox for treating exudative retinal disease?

A In real-world wet AMD dosing, multiple reports have documented that patients are not receiving the optimal number of injections based on current standard-of-care agents. The hope is that by developing more durable treatments, we are going to improve real-world outcomes.

Decreasing treatment burden is good, but at the same time, because we aren't dosing frequently enough in the real world, patients aren't achieving their long-term, maximum potential visual outcomes. More durable agents will deliver a meaningful advantage if they can address this real-world challenge. RS



KSI-301 is an intravitreally injected anti-VEGF antibody biopolymer conjugate of immunoglobin G1 antibody inert immune effector function (orange cluster) and branched high-molecular weight phosphorycholine polymer (light blue branches). (Courtesy Kodiak Sciences)

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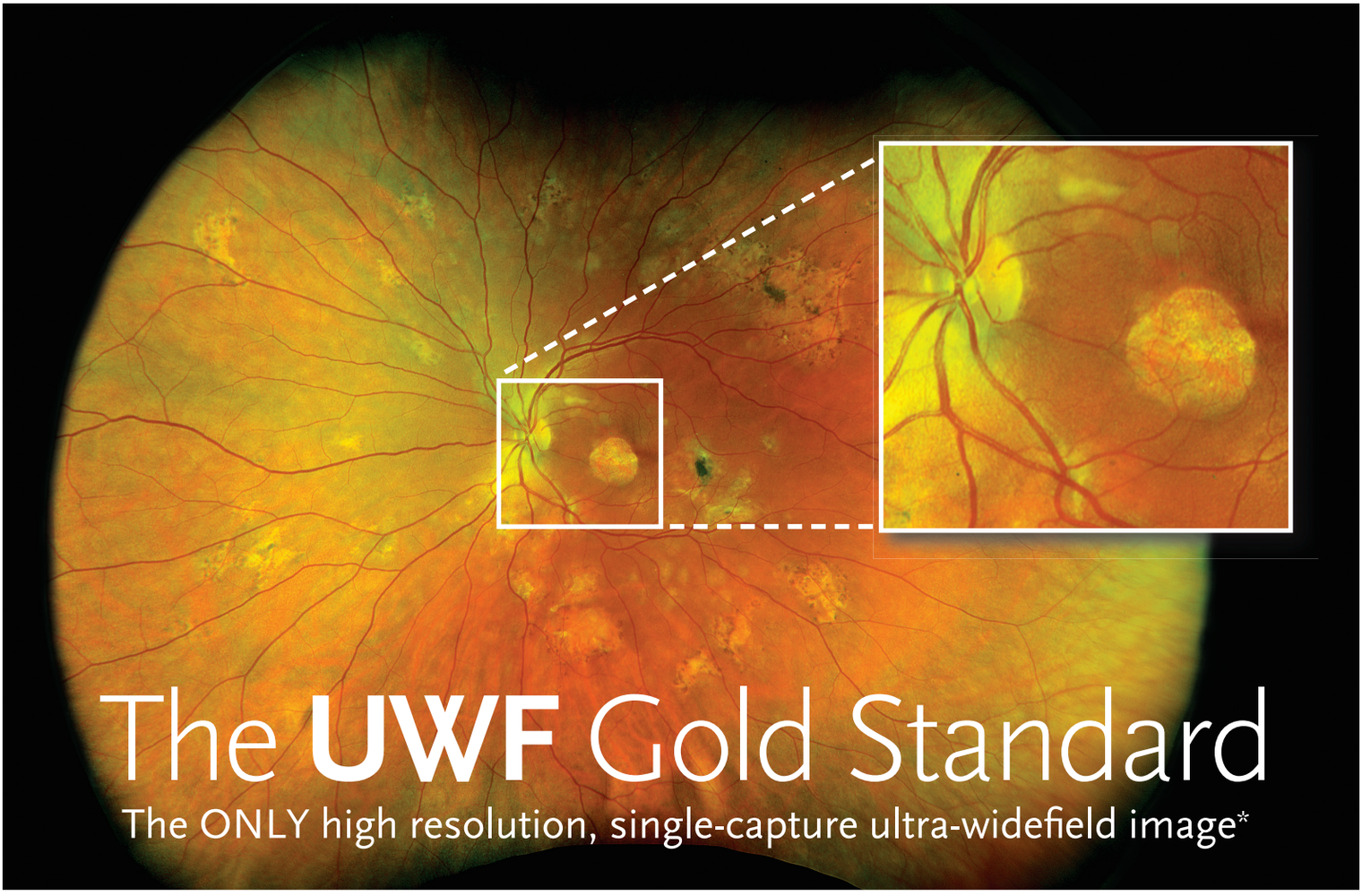

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