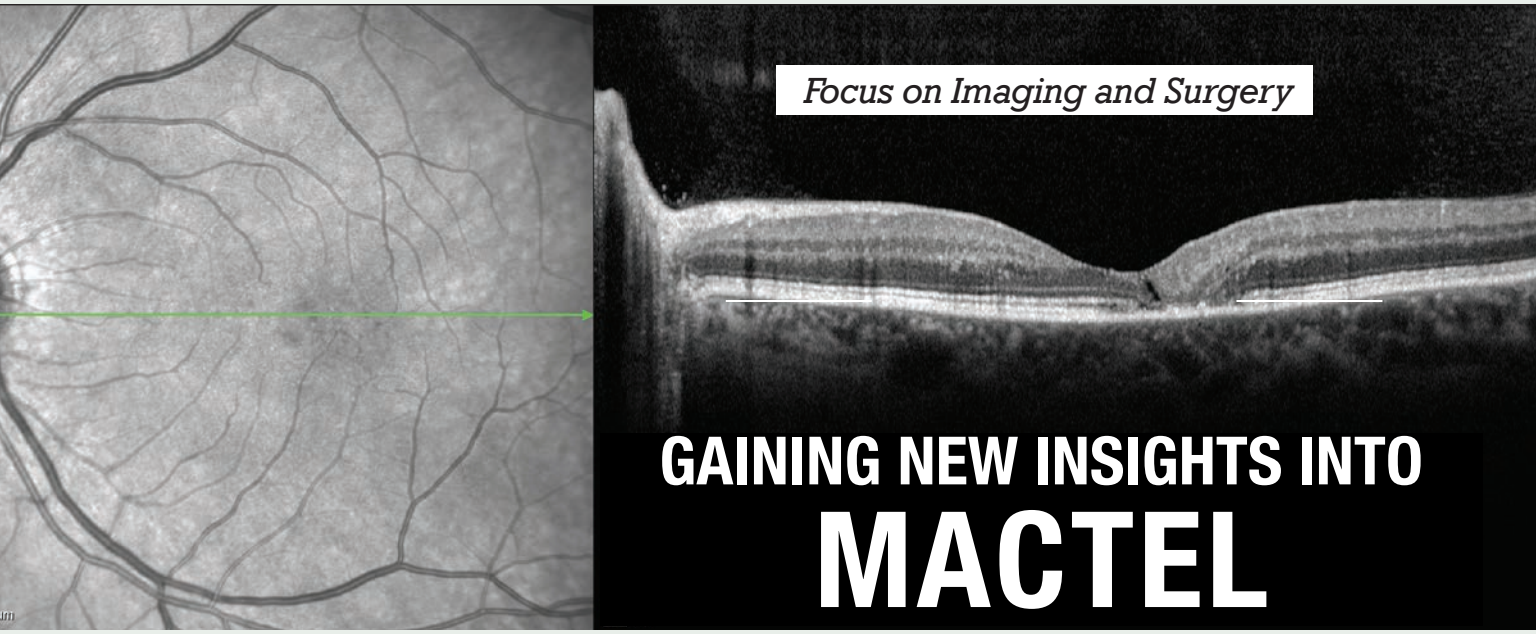
A PUBLICATION BY REVIEW of Ophthalmology

RETINA SPECIALIST

SEPTEMBER 2017



Focus on Imaging and Surgery

GAINING NEW INSIGHTS INTO MACTEL

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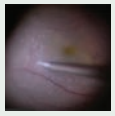
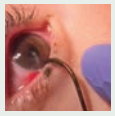
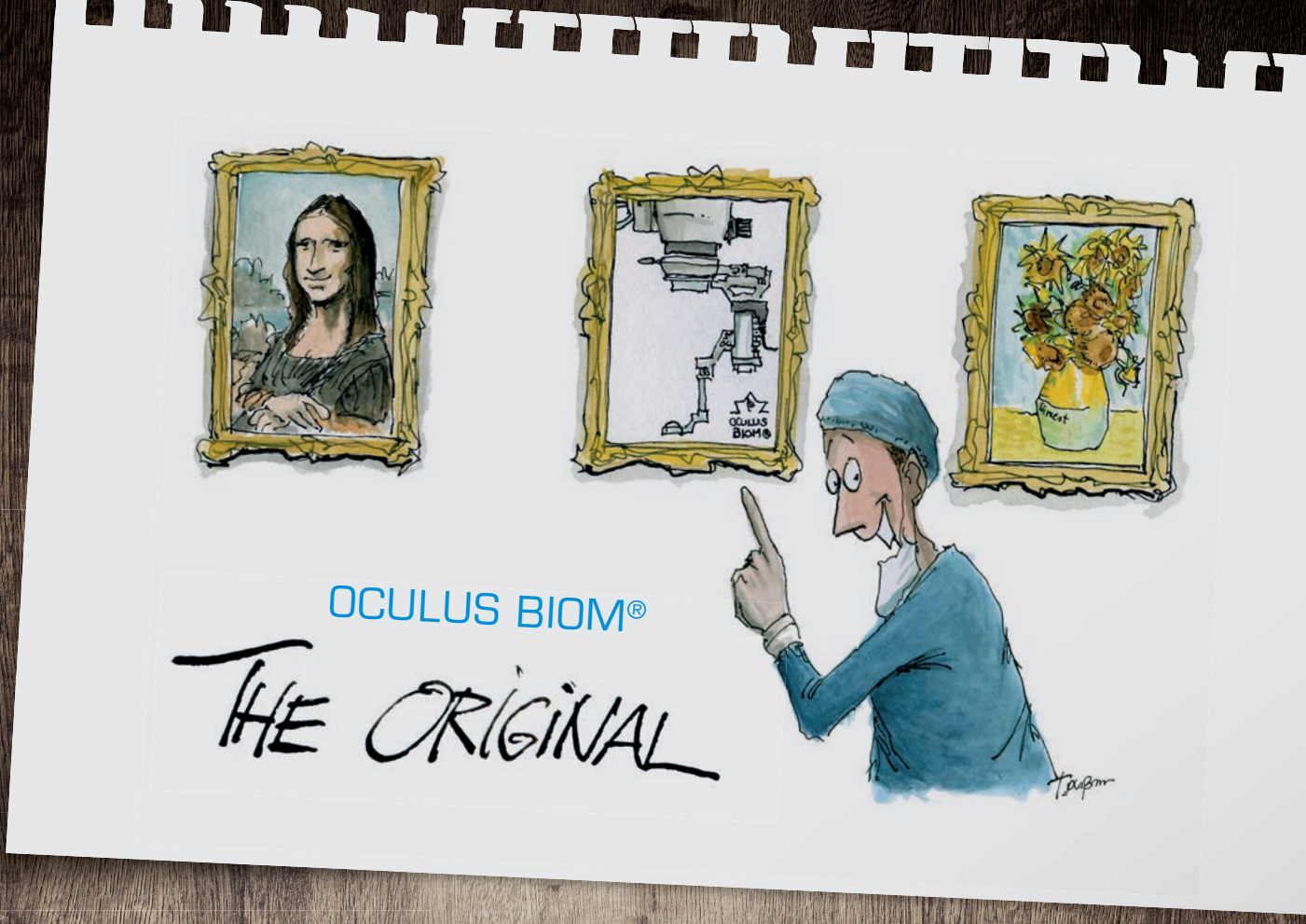


Triamcinolone Acetonide Assist For ILM Peeling – page 26



Advance-and-Cut Technique To Remove Fishhook – page 13



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By Charles C. Wykoff, MD, PhD

Flooding: Harvey, Irma and the Retina

I have water on my mind, or, more literally, in my house. Hurricane Harvey created one of the worst floods in U.S. history, unloading an estimated 33 trillion gallons of water, or more water than flows over Niagara Falls in 1.4 years.

While my home in Houston sustained no substantial damage, thousands of other people lost theirs, and, in some tragic cases, life itself. Multiple staff, friends and colleagues were evacuated, many by boat under the guidance of our National Guard. More than 100,000 families were displaced across Houston alone.

Experiencing such a powerfully destructive natural phenomenon up close is totally different from watching it on a screen. There is no off switch or silence button during the nightmares that can unfold as a hurricane like Harvey or Irma engulfs a region.

The outpouring of encouragement and support, both emotional and financial, has been remarkable. A simple, personal example came when a retina colleague in St. Louis called and said he and his partners had collected funds they were sending to our displaced employees who had lost everything. He said he'd been there; he knew how they felt. He wanted to lighten their load in a small way.

It's not quite the same, but in some ways we as retina specialists deal with flooding, or at least fluid where it shouldn't be, on a cellular level every day. Misplaced fluid is a hallmark of exudative retinal disease.

We have directly seen this flooding qualitatively for decades with fluorescein angiography. In this issue, Jaya Kumar, MD, and Justis Ehlers, MD, outline their vision of automated, quantitative assessment of widefield angiographic features such as leakage, microaneurysms and nonperfusion (*page 22*).

Vascular leakage even defines obscure diseases such as macular telangiectasia. Grant Comer, MD, of the University of Michigan, a leading center for the MacTel Project, updates us on the clinical characteristics of MacTel and a Phase III trial of ciliary neurotrophic factor bringing new hope to afflicted patients (*page 18*).

Rhegmatogenous retinal detachments are also manifestations of flooding, as liquefied vitreous flows through a retinal break, separating the neurosensory retina from the underlying retinal pigment epithelium. Tien Wong, MD, outlines his thoughts on surgical RD repair (*page 35*), and Kunihiko Akiyama, MD, from Tokyo describes his approach to minimizing postoperative epiretinal retinal membrane formation (*page 26*).

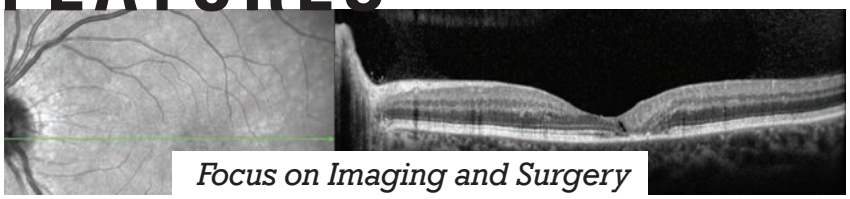
Floods come and go, some worse than others. Words do not capture the essence of the tragic situations that unfold in the wake of a powerful hurricane. I hope that the floodwaters, whether in your street, your house, your patients' retinas, or all of the above recede quickly and that affected areas come to thrive once again.

A PUBLICATION BY REVIEW

RETINA SPECIALIST

SEPTEMBER 2017

FEATURES



Focus on Imaging and Surgery

DEPARTMENTS

STRENGTH IN EVIDENCE

The efficacy and safety of LUCENTIS were rigorously studied in 10 clinical trials[1]*

LUCENTIS®
RANIBIZUMAB INJECTION

Approved for wet AMD, DR, DME, mCNV, and macular edema following RVO.

INDICATIONS

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

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS

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)
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

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

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

* The following randomized, double-masked clinical trials were conducted for the 5 LUCENTIS indications: **wAMD:** *MARINA*—Phase III, multicenter, 2-year, sham injection–controlled study; primary end point at 1 year. *ANCHOR*—Phase III, multicenter, 2-year, active treatment–controlled study; primary end point at 1 year. *PIER*—Phase IIIb, 2-year, sham injection–controlled study; primary end point at 1 year. *HARBOR*—Phase III, multicenter, 2-year, active treatment–controlled dose-response study; primary end point at 1 year. **DR and DME:** *RISE and RIDE*—Methodologically identical, Phase III, multicenter, 3-year, sham injection–controlled studies; primary end point at 2 years. *Protocol S*—Phase III, multicenter, 2-year, active-controlled study; key clinical outcomes at 2 years. **mCNV:** *RADIANCE*—Phase III, multicenter, 1-year, active-controlled study; key clinical outcomes at month 3. **RVO:** *BRAVO*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. *CRUISE*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months.[2-11]

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2017. **2.** Rosenfeld PJ, et al; MARINA Study Group. *N Engl J Med.* 2006;355:1419-1431. **3.** Brown DM, et al; ANCHOR Study Group. *Ophthalmology.* 2009;116:57-65. **4.** Regillo CD, et al; PIER Study Group. *Am J Ophthalmol.* 2008;145:239-248. **5.** Busbee BG, et al; HARBOR Study Group. *Ophthalmology.* 2013;120:1046-1056. **6.** Campochiaro PA, et al; BRAVO Investigators. *Ophthalmology.* 2010;117:1102-1112. **7.** Brown DM, et al; CRUISE Investigators. *Ophthalmology.* 2010;117:1124-1133. **8.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology.* 2013;120:2013-2022. **9.** Data on file. Genentech, Inc. South San Francisco, CA. **10.** Nguyen QD, et al; RISE and RIDE Research Group. *Ophthalmology.* 2012;119:789-801. **11.** 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

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 (2.7, 2.8) 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 (2.8 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	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control 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	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control 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(2) 2017
LUCENTIS® is a registered trademark of Genentech, Inc.

IN BRIEF

Second Sight Medical Products received conditional Food and Drug Administration approval to begin the feasibility clinical study of its Orion Cortical Visual Prosthesis System. The FDA also requested that the company conduct additional device testing and address outstanding questions. Second Sight's Argus II System provides electrical stimulation that bypasses defunct retinal cells and stimulates viable cells to induce visual perception in individuals with severe to profound retinitis pigmentosa.

Quantel Medical received FDA approval for the Easyret fully integrated 577-nm yellow photocoagulator, which has a range of settings for treatment of diabetic retinopathy, macular edema and central serous chorioretinopathy. In addition to SingleSpot treatment mode, Easyret has a Multispot mode for a pattern of simultaneous targets or the SubLiminal mode for a customized train of short pulses to precisely manage the thermal effect on targeted tissues.

The Phase III **Spectri** trial of lampalizumab failed to meet its primary endpoint, which was mean change in geographic atrophy lesion area compared to sham treatment at one year, **Genentech**, a member of the Roche Group, disclosed. Genentech expects to obtain results from the second Phase III trial of lampalizumab, Chroma, in November.

FILLY Trial Supports Complement Pathway Role in AMD Progression

Early results from the Phase II FILLY trial of the complement factor 3 (C3) inhibitor APL-2 (Apellis Pharmaceuticals) have confirmed the role the complement pathway has in the progression of age-related macular degeneration and offers some hope for the treatment of geographic atrophy (GA). Going forward, investigators hope to duplicate these results in Phase III trials, says principal investigator David Boyer, MD.

"Until now many people have thought the complement pathway may play role in geographic atrophy, but because of results of the FILLY trial it seems like the complement system does indeed offer some ability to treat the patients to prevent progression of geographic atrophy," says Dr. Boyer, of Retina-Vitreous Associates Medical Group in Los Angeles.

Geographic atrophy has confounded retina specialists because it remains a major cause of vision loss in patients with dry AMD and there is no Food and Drug Administration-approved treatment for it. Shortly after Apellis announced the FILLY trial results, Roche/Genentech disclosed that the Spectri trial, the first of two Phase III trials of lampalizumab for treatment of GA, failed to meet its primary endpoint, which was mean change in GA lesion area compared to sham treatment at one year.

The primary endpoint of FILLY was the change in GA lesion size from baseline to month 12 in the treatment group compared to sham. APL-2 was administered as an intravitreal injection in the study eye monthly or bimonthly for 12 months, followed by six months of monitoring after the end of treatment.

The early FILLY readout reported that monthly intravitreal injection of APL-2 showed a 29-percent reduction in the rate of GA lesion growth at 12 months compared to sham (p=0.008), and a 20-percent reduction with bimonthly administration (p=0.067).

A post-hoc analysis showed a greater effect during the second six months of the study: a reduction in the growth rate of GA lesions of 47 percent (p<0.001) with monthly administration, and a reduction of 33 percent (p=0.01) with bimonthly administration.

Says Dr. Boyer, "It seems that the difference between the treatment and sham groups really separates at the six-month level, and if that continues to go in a similar direction at 18 months, then this is a very powerful drug that may be able to help us treat patients with geographic atrophy long term."

Dr. Boyer notes that a number of studies are investigating the role the complement factor pathway in progress of AMD. "All point to the inflammatory mechanism or cascade as eventually causing activation and cell apoptosis, and continuing to progress the size of geographic atrophy lesions," Dr. Boyer says.

Adverse events in the FILLY trial were similar to those reported with other intravitreal therapies, Dr. Boyer notes.

The Phase II FILLY data is still fresh. "Hopefully in the next several months we can obtain more information and get a more complete idea if there's a certain genetic subtype that does better with this therapy," he says. The lampalizumab phase 2 Mahalo trial had a subgroup that responded better to therapy than the overall trial cohort. "Right at the moment the genetics are being evaluated to see if there's a genetic predisposition for a certain group of patients to do better," he says.

One of the more intriguing findings of the FILLY trial, Dr. Boyer explains, involved patients who received ALP-2 either monthly or bimonthly and had wet AMD in one eye and dry AMD in the fellow eye. Many of those patients eventually developed choroidal neovascularization. "They had a higher rate than the sham group," says Dr. Boyer, "and it was higher in the monthly than in the every-other-month treatment group, indicating that perhaps some degree of the transition from dry to wet is controlled by the complement pathway and blocking the complement pathway allows the patients to go on to develop wet AMD."

However, this was not so much the case in patients who had dry AMD with no wet AMD in the other eye. That will be further investigated in the forthcoming subanalysis of the FILLY data.

The FILLY trial involves 246 patients at 40 clinical sites, in the United States, Australia and New Zealand.

Investigational OCT Platform Eliminates Adaptive Optics

Researchers at MedUni Vienna have developed a new optical coherence tomography technique called Line Field-OCT that eliminates the use of adaptive optics to correct the occurring image defects in obtaining cellular resolution of the retina.

PhD student Laurin Ginner and Rainer Leitgeb of MedUni Vienna reported on the new LF-OCT technology in a study published last month in the journal Optica.[1]

"With our new method, we can make the corrections digitally without the need for expensive, hardware-based adaptive optics," Mr. Ginner says. "Due to the line illumination used, very fast image rates are possible which are extremely important for these corrections. This allows us to correct image defects over the entire three-dimensional volume of the retina."

The line lighting works similar to a scanner in that a light strip "scans" the eye. Individual photoreceptors, capillary blood vessels and individual nerve fibers can be resolved in the same receptacle. Furthermore, refocusing is possible, as are reorientation and digital post-processing of the obtained image data in order to provide highest resolution results for the diagnostics.

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OCT-Eh? Canadian for Macular Imaging

How OCT angiography can alter the management approach to macular disease.

By Roy Alon, MD, Michael H. Brent, MD, FRCSC

Optical coherence tomography angiography (OCT-A) is a new technology that demonstrates macular, retinal and choroidal blood flow without using intravenous dye. Our clinic recently started using OCT-A (Angiovue, Optovue). Here, We present two interesting cases in which OCT-A was beneficial in guiding us in diagnosis and management of macular disease.

In the first case, OCT-A helped us to consider a different etiology for a macular hemorrhage prior to performing an intravenous fluorescein angiography (IVFA). Post-IVFA, the diagnosis was unchanged. In the second case, OCT-A demonstrated abnormal flow in the choriocapillaris, representing choroidal neovascularization (CNV), which interestingly, was not identified on IVFA. A positive response to treatment suggests that CNV was present.

Case 1: OCT-A Alters Diagnosis

An 87-year-old woman who's had non-insulin-dependent diabetes for seven years was referred to our clinic in July 2016. She had a history of wet age-related macular degeneration in her right eye, and had been on a treat-and-extend regimen with ranibizumab (Lucentis, Roche/Genentech) since 2013. She had four intravitreal ranibizumab injections in her left eye in 2013-2014 for reasons that were unclear, but most likely due to diabetic macular edema, but had no further injections in the left eye since.

Her visual acuity (VA) was counting fingers (CF) and 20/70 OD and OS, respectively. Geographic atrophy and a macular scar were present in the macula OD, and drusen and a macular scar OS. No signs of diabetic retinopathy were evident in either eye. OCT showed no evidence of intraretinal (IRF) or subretinal (SRF) fluid in either macula. We made the decision to continue intravitreal ranibizumab OD with interval extension to 10 weeks and observation OS.

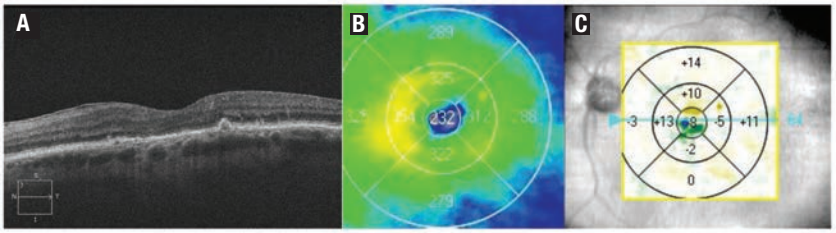


Figure 1. An optical coherence tomography scan OS (A) demonstrates epiretinal membrane and drusen but no intra- or subretinal fluid. Macular thickness map (B) demonstrates normal central retinal thickness (CRT), while retinal change analysis (C) shows no significant change in CRT.

We saw the patient on two subsequent occasions, extending the interval of ranibizumab to 12 weeks OD and a stable macula OS. On follow-up in March 2017, she reported no visual changes, and her VA was stable at CF and 20/50 OD and OS, respectively.

Examination revealed a new small

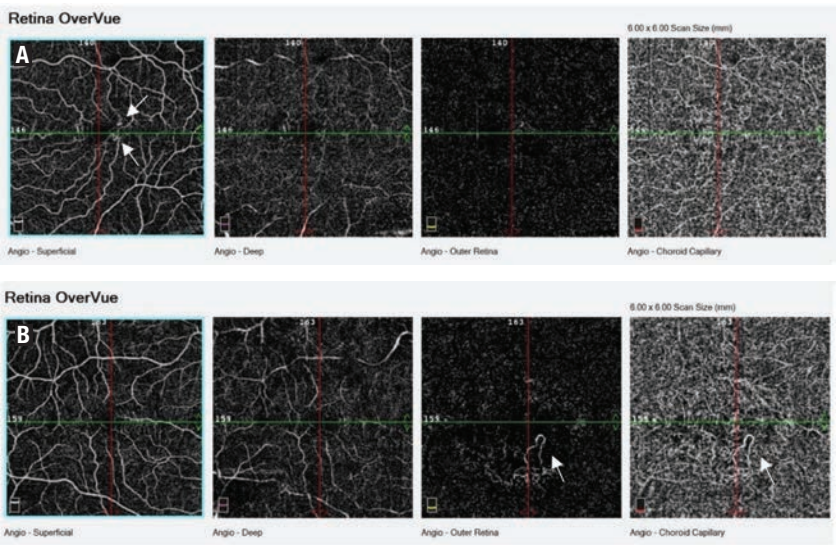


Figure 2. Optical coherence tomography angiography (OCT-A) OS (A) demonstrates no choroidal neovascularization (CNF) in the outer retina/choroid. Dilatation of blood vessels (microaneurysms) appears in the superficial vascular plexus (arrows). OCT-A OD (B) shows quiescent CNV (arrows) in the outer retina and choroid.

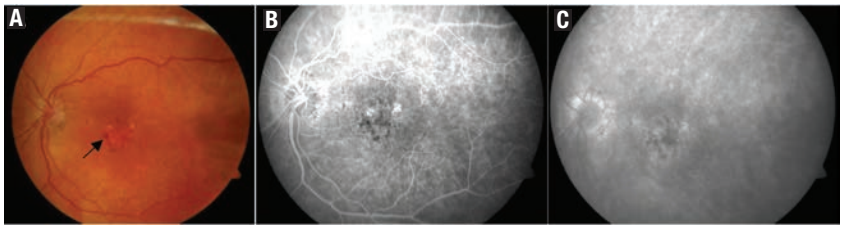


Figure 3. Color photo OS (A) demonstrates a small hemorrhage (arrow), but early (B) and late (C) fluorescein angiography show no leakage.

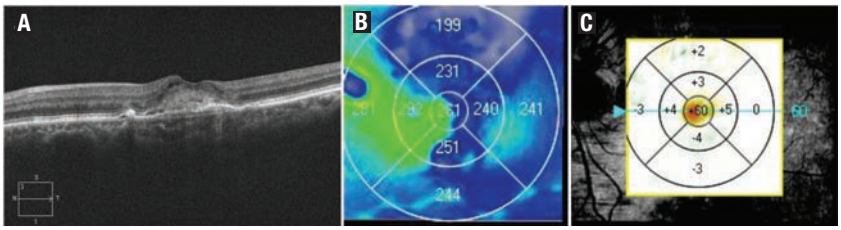


Figure 4. Optical coherence tomography (A) demonstrates hyper-reflectivity with intraretinal cyst and fluid (choroidal neovascularization). Macular thickness imaging (B) demonstrates normal central retinal thickness while retinal change analysis (C) shows significant increase in central retinal thickness.

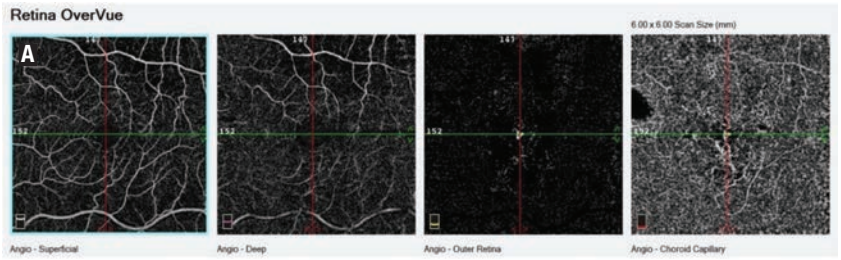
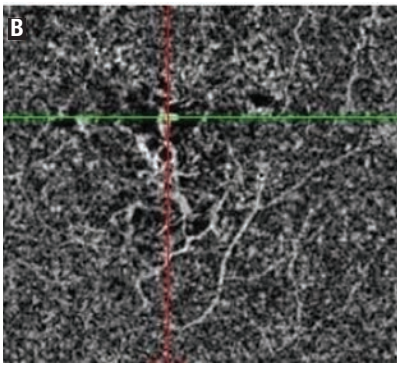


Figure 5. Optical coherence tomography angiography OS (A) demonstrates a filamentous type of choroidal neovascularization that often appears in chronic central serous chorioretinopathy, observed in the choroid. Magnification (B) shows the finding in greater detail.



hemorrhage in the left macula. OCT revealed no evidence of IRF/SRF (*Figure 1, page 9*), and central retinal thickness (CRT) was stable in both eyes. We recommended an IVFA, but the patient hesitated. She did consent to noninvasive OCT-A, which failed to show any abnormal flow in the choriocapillaris or outer retina (ie, CNV), but did demonstrate dilatation of blood vessels in the superficial capillary plexus, suggestive of a microaneurysm. OCT-A showed a quiescent treated CNV OD (*Figure 2, page 9*).

Prior to OCT-A imaging, our presumptive diagnosis was new wet AMD OS. Supporting this were wet AMD in her fellow eye, the clinical appearance of macular drusen, pigmentary changes, hemorrhage and patches of atrophy in the macula OS, and the fact that no diabetic retinopathy had been present in either eye. Main arguments against this diagnosis were stable VA OS, and the lack of SRF/IRF on OCT and OCT-A.

After discussing the clinical and

(Continued on page 17)

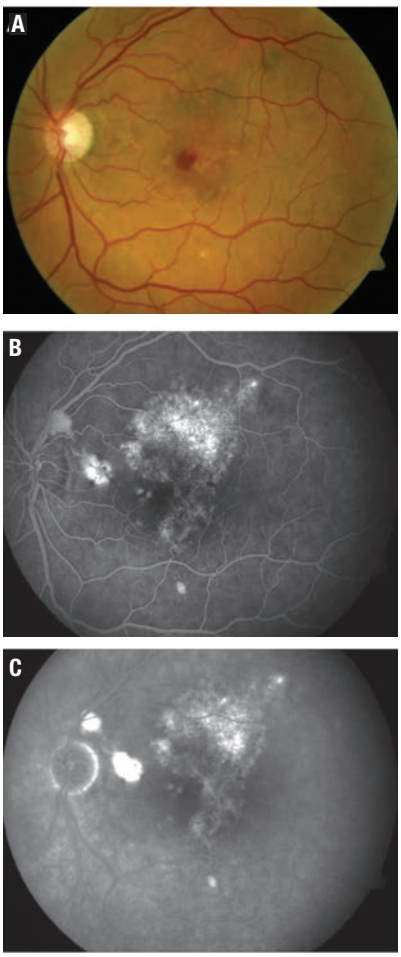


Figure 6. Color photo OS (A) shows macular hemorrhage, but early (B) and late (C) fluorescein angiography do not exhibit any leakage.

Don't Miss the Disc

Clues to the etiology of a unilateral maculopathy are found beyond the retina.

By Steven Saraf, MD, and Marcela M. Estrada, MD.

A 68-year-old woman presented to our clinic for a second opinion regarding areas of "geographic atrophy" in her right eye identified at her last annual diabetic eye exam. An outside retinal specialist rendered a presumptive diagnosis of atypical retinal degeneration vs. inactive central serous chorioretinopathy.

She complained of slowly progressive, diffuse blurry vision over the past year, worse in her right eye and exacerbated by dim lighting. She denied scotomas, metamorphopsia, progressive nyctalopia, or any personal or family history of retinal degeneration. Her ocular history was significant for cataracts and mild myopia without a history of myopic degeneration. She had no known history of diabetic retinopathy or macular edema.

She had been told her symptoms might be secondary to cataract with the intent to have cataract extraction soon. Her medical history included well-controlled type 2 diabetes, hypertension, hypercholesterolemia and remote bariatric surgery. She was a former smoker. A review of systems was unremarkable.

Examination Findings

Best-corrected visual acuity was 20/40 OD and 20/20 OS. Intraocular pressures were normal. We also noted bilateral nuclear sclerotic and cortical cataracts; worse in the right eye.

Fundus examination of the right eye revealed an anomalous-appearing nerve with nasal tilt and inferonasal optic pit near the rim at 4 o'clock along with a 0.25-disc diameter patch of retinal pigment epithelium atrophy within the nasal macula (*Figure A*).

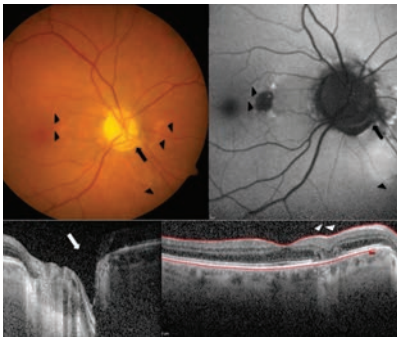


Figure. Color photo of the right eye (A) shows the inferonasal optic disc pit (arrow) and pigmentary changes in the nasal macula and inferior peripapillary retina (arrowheads). Fundus autofluorescence (B) shows patchy hypo- and hyperautofluorescent lesion in the nasal macula corresponding to fundus photos. Optical coherence tomography (OCT) of the right eye nerve fiber layer shows inferotemporal cavitation (C, arrow), while OCT of the right macula (D) shows focal outer retinal atrophy (arrowheads).

Foveal light reflex was intact without edema or hemorrhage, and retinal vessels were normal. We noted similar retinal pigment epithelium changes in the nasal and inferonasal peripapillary retina (*Figure A*). Fundus examination of the fellow eye revealed a normal optic nerve except for three small areas of pigmented lattice in the periphery without holes or tears. We also noted posterior vitreous detachments in both eyes.

What the Workup Revealed

Optical coherence tomography (OCT) of the right macula demonstrated normal foveal contour and retinal laminations. A focal, well-circumscribed patch of outer retinal atrophy was present in the nasal macula, including loss of the ellipsoid zone and retinal pigment epithelium with underlying transmission defect (*Figure D*). No intraretinal or subretinal fluid was evident. OCT of the right optic nerve showed a pit visualized on cross section with retinal nerve fiber layer thinning in the inferonasal sector (*Figure C*).

Fundus autofluorescence of the right eye demonstrated focal hypoautofluorescence in the nasal macula corresponding to the area of outer retinal atrophy. Two smaller areas of hyperautofluorescence appeared superior and inferior to the atrophy. Patches of hyperautofluorescence were also located nasally and inferonasally to the disc (*Figure B*).

Diagnosis and Management

This patient presented with asymptomatic unilateral maculopathy in the setting of an ipsilateral optic disc pit with adjacent peripapillary retinal pigment epithelial changes. Taken together, her findings most likely represent quiescent optic pit maculopathy. Other possibilities include inactive central serous retinopathy, pattern dystrophy or a unilateral age-related macular degeneration variant. We recommended she continue regular follow-up with a retina specialist and to self-monitor with an Amsler grid. There was no contraindication to proceeding with cataract surgery as planned in the affected eye.

Discussion

Optic pits are rare, congenital defects with an estimated incidence of 1:11,000 ophthalmology patient visits.[1] They likely arise from failed closure of the embryonic fissure, although their

etiology remains controversial.[1–5]

Optic pits present as small, hypopigmented, yellow or gray-white, oval or round excavations typically found in the inferotemporal portion of the optic disc margin. Eighty-five to 90 percent of optic pits are unilateral and the majority of affected nerves have only one pit per disc.[1] The differential for optic pits includes glaucomatous optic neuropathy, optic nerve coloboma, choroidal and scleral crescent, tilted disc syndrome, circumpapillary staphyloma and hypoplastic disc.[2]

Optic pits are generally asymptomatic and incidentally identified on routine exam, but can be associated with an enlarged blind spot, arcuate scotoma or cecocentral scotoma corresponding with their location on the optic disc in the absence of other findings.[1] Related central vision defects include decreased visual acuity, dyschromotopsia, metamorphopsia, micropsia or relative/absolute central scotomas, and are nearly exclusively associated with secondary macular pathology.[1–5] In one case series, 66 percent of optic pits demonstrated macular pathology, which included schisis-like intraretinal fluid cysts, subretinal fluid and degenerative pigmentary changes thought to be remnants of longstanding serous maculopathy similar to that seen in our patient.[1] In other case series, patients presenting with optic pit maculopathy typically had visual acuity worse than 20/70 in the affected eye.[2]

Spontaneous resolution of optic pit maculopathy is estimated to occur in 25 percent of cases, with excellent recovery of vision.[2]

Although recurrence of optic pit maculopathy has been reported, no triggers for initial development or recurrence are known.[4] Optic pits typically become symptomatic in the third or fourth decade, but case reports demonstrate a wide range of onset from infancy to the ninth decade.[4] The origin of optic pit fluid remains unclear, but leading theories implicate liquid vitreous, cerebrospinal fluid, leaky blood vessels at the base of the optic pit or fluid from the orbital space surrounding the dura.[2–5]

The pathogenesis for secondary maculopathy is equally controversial as only one-third of cases show a direct communication between the optic pit and macular pathology.[5] Two commonly proposed mechanisms for development of maculopathy are:

- Fluctuations in the gradient between intraocular and intracranial pressures that direct movement of fluid through the cavitation and into/under the retina.
- Vitreous traction, made worse by progressive vitreous liquefaction in the third and fourth decade.[2-5]

As a result of the latter, most treatment options are aimed at inducing posterior vitreous detachment, reducing traction and disrupting communication between the optic pit and macula. However, due to the lack of comparative treatment studies of this rare phenomenon, no established treatment guidelines exist, although surgical intervention is generally recommended with active serous maculopathy due to the poor visual prognosis.

Acceptable surgical options, often performed in combination, include pars plana vitrectomy, internal limiting membrane peel, gas tamponade (C3F8 or SF6), laser photocoagulation applied to the temporal margin of the disc and macular buckling.[4] Due to the paucity of supporting literature, prophylactic treatment is generally not recommended for incidentally identified optic pits without maculopathy or for quiescent maculopathy without fluid.[4]

When evaluating patients with retinal pathology, maintaining a systematic approach to the dilated fundus exam, including careful evaluation of the optic disc, is prudent. Although rare, optic pit maculopathy should be included in the differential for serous maculopathy at any age, but particularly in patients in the third and fourth decade and for peripapillary atrophic changes associated with an anomalous disc. Although prognosis is poor without intervention, case series of surgical interventions have shown excellent results and visual recovery, although long-term data and comparative studies are needed.

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UW Medicine EYE INSTITUTE

Dr. Olmos de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington, Seattle, where Dr. Estrada is a second-year ophthalmology resident and Dr. Saraf a retina fellow.

By Paul Hahn, MD, PhD »

Advance-and-Cut for Fishhook Removal

Having large-gauge wire cutters at the outside is critical. ***With Jayanth Sridhar, MD, Louis Cai, BS, Harry W. Flynn, Jr., MD, and Arunan Sivalingam MD***

Fishing-related eye injuries are an important cause of sports-related eye trauma.[1] Here, experts from the Bascom Palmer Eye Institute and Mid Atlantic Retina share pearls for management and surgical removal of a barbed fishhook.

Evaluation and Preparation

Patients with intraocular fishhook injuries will often not tolerate adequate in-office examination. Imaging studies including X-ray and/or CT scanning may be useful to localize the foreign body. Keep these patients NPO and arrange for emergent evaluation under anesthesia in the operating room and initiate a typical ruptured globe protocol. Administer systemic and intraocular antibiotics and tetanus (if not up to date), and avoid unnecessary manipulation of the eyelids and globe.

Surgery

When planning for removal of a fishhook from an eye, consider these situations in advance:

• ***Is the hook barbed?*** Barbed hooks may preclude safe removal from the original entry wound, because retrograde removal of the barb will significantly damage the wound architecture.

• ***Is there an exit site?*** With a barbed hook, it becomes important to note if there is an exit wound. An "advance-and-cut" technique is useful when approaching barbed fishhook removal (*Figure*).[2] It involves rotating and advancing the hook to pass the barb through an exit wound to expose it for cutting and removal. Then the residual hook (with the barb removed) may be withdrawn through the original entry wound and removed from the eye. Although this technique requires additional manipulation within the eye to expose the barb for cutting, it minimizes the risk of dragging the barb backwards through the entry wound and gaping it. If there is no exit wound, it still may be advisable to create a controlled exit wound with a blade to perform this technique.

• ***How thick are the hook and barb?*** Often the patient or family members and friends will have an identical hook or a picture to show you. Even without this useful information, plan for the worst and be prepared with the appropriate tools. Most ophthalmology instruments will not be able to cut even small-gauge hooks. Ask the operating room staff to obtain sterile large-gauge wire cutters or rod cutters that may be available in otolaryngology, neurosurgery or orthopedic surgical trays. Having these available at the start of the case will help avoid unnecessary delays (and sweating on the part of the surgeon) if one's first option fails to cut the barb.

As always, surgical planning is the key to success. While penetrating or perforating ocular injuries are often associated with a poor prognosis, this advance-and-cut technique can help elegantly remove a barbed fishhook to maximize visual outcomes. We hope not to see this, but should be prepared if we do!

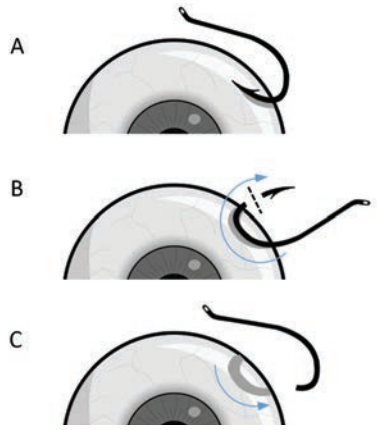
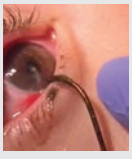


Figure. In the advance and cut maneuver the fishhook is advanced through an exit wound (A), the barb is cut (B), and the fishhook is retracted through the original entry wound. Courtesy Louis Cai, BS, and Justin Ma, BS

View the Video



Watch as Drs. Sridhar and Sivalingam perform an advance-and-cut technique to safely remove a perforating intraocular fishhook. Available at: http://bit.ly/RS_VideoPearl_003

Dr. Hahn is an associate at New Jersey Retina in Teaneck. Dr. Sridhar is assistant professor of ophthalmology at Bascom Palmer Eye Institute, Miami, and formerly a fellow at Wills Eye Hospital, Philadelphia. Mr. Cai is a medical student at the University of Miami Miller School of Medicine. Dr. Flynn holds the J. Donald M. Gass Distinguished Chair in Ophthalmology at Bascom Palmer. Dr. Sivalingam is with Mid Atlantic Retina and fellowship director of the retina service at Wills Eye Hospital, Philadelphia.

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Series: Beyond the Retina

HOW MIGS IS BRIDGING THE EFFICACY GAP IN GLAUCOMA

An update on the state of the rapidly advancing field of minimally invasive glaucoma surgery.

By Jesse B. McKey, MD

For decades, the gap in the ratio of safety to efficacy between topical therapies and surgery for glaucoma has posed a conundrum to clinicians faced with the treatment of mild-to-moderate glaucoma that is not completely controlled with eye drops or selective laser trabeculoplasty. However, the advent of minimally invasive glaucoma surgery (MIGS) technology is helping to bridge this gap, offering increased efficacy and better safety profiles.

The milieu of MIGS comprises several different procedures and devices, targeting both the trabecular meshwork and uveoscleral aqueous outflow pathways. In the United States, most MIGS procedures are indicated only at the time of concurrent cataract surgery, although certain technologies also carry the indication as a standalone procedure. This third article in the series "Beyond the Retina" explores the most common MIGS technologies and their unique indications and attributes. The full scope of the rapidly changing field of MIGS extends beyond this review.

The Conundrum of Glaucoma

In upcoming decades, the prevalence of glaucoma is only expected to increase as the population ages.[1] Of the various forms of glaucoma—acute and chronic angle closure, secondary open-angle, secondary angle closure, juvenile and congenital—primary open-angle glaucoma (POAG) is by far the most common, accounting for approximately 74 percent of all cases worldwide.[2]

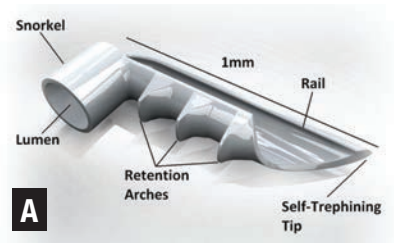
The Ocular Hypertension Treatment Study (OHTS) outlined importance of early intraocular pressure (IOP) control in the treatment of glaucoma.[3] OHTS showed that eyes with untreated ocular hypertension have a 9.5 percent rate of glaucomatous progression over five years, and decreasing IOP by 20 percent reduces the rate of progression to 4.4 percent. Treatment for mild/moderate POAG has traditionally focused on eye drops and selective laser trabeculoplasty (SLT). The safety profile of these treatments is favorable, but the real-world efficacy less so.

Noncompliance with glaucoma regimens is notoriously widespread, with rates ranging from 25 to 80 percent depending on the number of medications and drop frequencies.[4] The problem is multifactorial, as ocular side effects and rising medication costs also contribute to poor compliance. While the goal of SLT is to reduce these issues to a degree, the effect can be variable and diminishes

ABOUT THE AUTHOR

Dr. McKey practices at Whitsett Vision Group, Houston, specializing in cataract and refractive surgery as well as new minimally invasive glaucoma surgery (MIGS) technology.

Disclosure: Dr. McKey has no relevant conflicts to disclose.



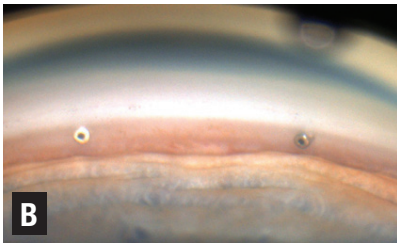


Figure 1. A schematic of iStent (Glaukos) (A) and a gonioscopic image (B) of the iStent successfully implanted in the nasal trabecular meshwork.

over time, with the rate of patients achieving a 20-percent reduction in IOP at five years reported to be between 55 and 72 percent.[5] Surgery, primarily trabeculectomy and tube-shunting procedures, remains the gold standard for more severe POAG. While these are some of the most effective procedures in terms of IOP control, rates of intra- and postoperative complications are not insignificant.[6] MIGS has emerged as a solution to these challenges.

Aqueous Outflow Pathways

The ciliary body epithelium produces aqueous humor in the posterior chamber and flows through the pupil into the anterior chamber. The aqueous exits the eye either through the trabecular meshwork (TM) into Schlemm's canal and aqueous veins (conventional pathway) or through the ciliary muscle and other downstream tissues (uveoscleral pathway).

In the conventional pathway, as aqueous humor moves from the interior part of the TM to the exterior side (juxtacanalicular) adjacent to the inner wall of Schlemm's canal, the porosity of the tissue decreases. W. Morgan Grant, MD, reported in the 1950s that the resistance to aqueous outflow occurs at the junction where the TM meets the inner wall of Schlemm's canal.[7] MIGS devices that target the conventional pathway, such as the iStent (Glaukos, *Figure 1*) and Kahook Dual Blade (New World Medical, *Figure 2*), seek to decrease this outflow resistance to lower IOP.

In the uveoscleral outflow pathway, aqueous humor enters the ciliary muscle and exits through the supraciliary space and across the anterior or posterior sclera, through the emissarial canals around the vortex veins or into the choroidal vessels. We now know that uveoscleral drainage can account for up to 60 percent of the total aqueous humor drainage.[8] MIGS devices that focus on the uveoscleral pathway include the CyPass (Alcon, *Figure 3, page 16*) and, to an extent, the XEN45 gel stent (Allergan).

Targeting Conventional Pathway

• ***iStent.*** Approved by the Food and Drug Administration in 2012, the Glaukos iStent (*Figure 1A*) was one of the first MIGS devices to reach the U.S. market. It is an L-shaped trabecular stent made of heparin-coated titanium, and it is the smallest MIGS device at 0.3 mm by 1 mm. The device is inserted via an ab interno approach through the trabecular meshwork and seated into Schlemm's canal in order to increase aqueous outflow. Currently in the United States, iStent is only approved for implantation at the time of cataract surgery.

Initial efficacy studies are promising. In 2015, a study comparing cataract surgery combined with iStent implantation to cataract surgery alone showed that 68 percent of patients in the iStent treatment group met the primary endpoint of IOP < 21 mmHg with no medications at one year, compared with only 50 percent of subjects receiving cataract surgery only (p=0.004).[9] A subsequent meta-analysis including 2,495 patients in more than 30 studies concluded that

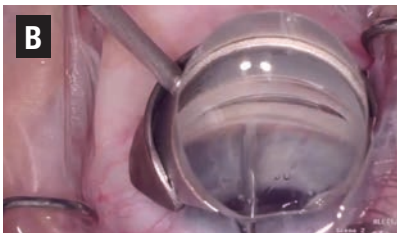


Figure 2. Schematic (A) shows the proprietary footplate of the Kahook Dual Blade (KDB) designed to simultaneously raise and excise trabecular meshwork tissue, and a gonioscopic image (B) of the KDB advancing across the nasal trabecular meshwork.

Take-home Point

The advent of minimally invasive glaucoma surgery—MIGS—provides an alternative to drop therapy with a higher level of efficacy while making minimal compromises in overall safety. This article explores the pathophysiology of glaucoma, and reviews the MIGS devices available in the United States and their mechanisms of action. Moving forward, the ever-expanding range of devices and procedures affords the opportunity to further customize glaucoma treatment to the individual and at the same time greatly reduce the burden of patient compliance.

combined cataract surgery and iStent implantation reduced IOP by 9 percent compared with a 4 percent reduction after cataract surgery alone.[10]

A newer-generation iStent available in Europe and other countries has been modified to allow for the implantation of two stents in an eye during the same procedure. A meta-analysis of eyes receiving two iStents showed a 27-percent reduction in IOP from preoperative baseline.[10] Safety profiles for combined cataract surgery/iStent implantation are similar to cataract surgery alone, and given that aqueous outflow through the trabecular pathway is limited by episcleral venous pressure, hypotony is extremely rare.[10]

Postoperative care for patients receiving iStent implantation does not differ significantly from standard cataract surgery in terms of drop schedules and follow-up, although a final steady-state reduction in IOP may not occur for several weeks.

• ***Kahook Dual Blade (KDB).*** Introduced in the United States in late 2015, the KDB (*Figure 2, page 15*) is a single-use ophthalmic blade used to precisely perform a goniotomy through an ab interno approach. The blade platform is specially designed to lift and excise a strip of trabecular meshwork as it is advanced across the angle. In the United States, it is approved for use in conjunction with cataract surgery as well as a standalone procedure.

A multicenter cohort study of 122 eyes at eight centers revealed that combined cataract surgery with the KDB procedure yielded an average postoperative IOP of 13 mmHg compared to the preoperative baseline of 17.4 mmHg (p<0.001).[11] The mean glaucoma medication burden was also significantly reduced compared to baseline (p<0.001). In 96 percent of cases, surgeons agreed or strongly agreed that the use of the KDB was straightforward, entry into Schlemm's canal was uncomplicated, and advancement along the treatment pathway was without difficulty.

As with the iStent, postoperative care for the KDB is similar to standard cataract surgery.

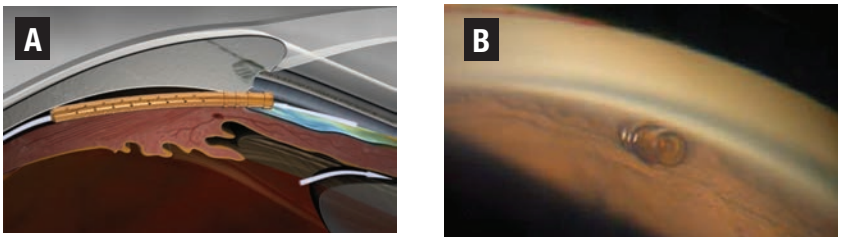


Figure 3. Depiction of the CyPass Micro-Stent (A) shunting aqueous fluid into the suprachoroidal space (A), and a gonioscopic image (B) of the CyPass post-implant.

Targeting Uveoscleral Outflow

• ***CyPass Micro-Stent.*** One of the newer MIGS devices, having been approved in summer 2016, the CyPass Micro-Stent (*Figure 3*) is a fenestrated microstent 6.35 mm long and 500 µm in diameter, composed of biocompatible polyimide material that is magnetic resonance safe. It is inserted into the angle between the scleral spur and ciliary body, creating a direct communication between the anterior chamber and the suprachoroidal space. It is indicated for placement at the time of cataract surgery to treat mild-to-moderate OAG.

The multicenter, randomized COMPASS trial enrolled more than 500 patients.[12] Preoperatively, all patients had mild-to-moderate POAG with unmedicated IOP between 21 and 33 mmHg. At the two-year endpoint, patients receiving phacoemulsification combined with CyPass implantation showed an average drop in IOP of 7 mmHg compared with 5.3 mmHg in the control group receiving phacoemulsification alone. In addition, 93 percent of patients in the CyPass group remained medication-free at two years. No severe adverse events occurred throughout the study compared with cataract surgery alone. While hypotony is a theoretical concern in any device that shunts to the suprachoroidal space, the COMPASS investigators did not report any clinical hypotony. As with other MIGS procedures, postoperative care is no different than with standard cataract surgery.

Targeting Other Mechanisms

• ***Endoscopic Cyclophotocoagulation (ECP).*** ECP attempts to decrease the rate of aqueous production in the ciliary body epithelium by using a curved endoscopic probe that contains a light source, a camera and a semiconductor diode laser. This technology allows direct visualization of the ciliary epithelium, allowing the laser energy to be precisely delivered to the ciliary processes for 270° to 360°, thus limiting damage to the underlying ciliary body and surrounding tissues. For this reason, it is widely accepted as much safer than other cyclodestructive procedures. In the United States, it is performed in conjunction with cataract surgery.

A randomized controlled trial in 626 medically controlled glaucoma patients reported that phacoemulsification combined with ECP was superior to phacoemulsification alone in lowering IOP and decreasing glaucoma medication burden.[13] These au-

thors reported no serious complications in either group, and the rates of cystoid macular edema were the same in both groups. Postoperative care does not differ significantly from that of standard cataract surgery.

• ***Xen Gel Stent.*** This is another one of the newer MIGS devices in the United States, having been approved in the fall of 2016. Xen Gel is a soft, permanent, subconjunctival implant approximately 6 mm long derived from a collagen-based, noninflammatory gelatin. It is inserted using a disposable Xen injector through a small, self-sealing corneal incision into the subconjunctival space via an ab interno approach. Flexible material allows it to conform to ocular tissue, possibly minimizing many of the issues seen with synthetic materials such as migration, erosion and corneal endothelial damage. While the Xen Gel Stent has the potential to benefit a wide range of patients, it is currently marketed for the treatment of refractory glaucoma.

A trial of refractory glaucoma patients showed that the Xen Gel reduced IOP from a mean medicated baseline of 25.1 (+ 3.7) mmHg to 15.9 (+ 5.2) mmHg at 12 months postoperatively.[14] The mean baseline number of IOP-lowering medications was 3.5 vs. an average use of 1.7 at 12 months. Following surgical implantation, providers will need to be comfortable with issues regarding bleb management in addition to standard postoperative cataract care.

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(Continued from page 10)

imaging findings with our patient, she consented to an IVFA to clarify the need for anti-VEGF therapy in the left eye. IVFA failed to demonstrate leakage/CNV, supporting the findings on OCT-A (*Figure 3, page 10*). Based on these findings, we chose not to initiate anti-VEGF therapy and instead opted for observation. On her last follow-up in June 2017, she was clinically stable with no sign of wet AMD.

Case 2: Abnormal Flow

This case involves a 55-year-old man with recurrent central serous chorioretinopathy (CSCR) in both eyes, more active in the left. In 2010 he was treated with reduced fluence photodynamic therapy in the left eye, with complete resolution of his SRF. He had recurrence of CSCR in the left eye in 2016 and received thermal laser treatment, with complete resolution of SRF. CSCR recurred in late 2016, which resolved spontaneously. Over time, VA had deteriorated to 20/400 OD due to retinal pigment epithelium atrophy. Vision OS—his good eye—was stable at 20/40.

He presented to our clinic in March 2017 with a two-week history of decreased vision OS. VA had decreased by two lines to 20/60, and a new macular hemorrhage was present OS. OCT imaging revealed a new hyper-reflective area, with small intraretinal cysts and overlying fluid. The CRT had increased by 60 µm to 261 µm (*Figure 4, page 10*). OCT-A demonstrated flow in the choriocapillaris layer, representing a vascular network. This appeared to be a filamentous-type CNV, often seen in chronic CSCR (*Figure 5, page 10*).

The findings on OCT and OCT-A were consistent with CNV. We completed multimodal imaging by performing an IVFA and, interestingly, found no leakage (CNV) (*Figure 6, page 10*). This patient had a diagnosis of chronic CSCR, with a new macular hemorrhage, intraretinal fluid on OCT, CNV on OCT-A, but no leakage on IVFA.

Our presumptive diagnosis was CNV complicating chronic CSR, and the patient was started on aflibercept (Eylea, Regeneron) OD. After three intravitreal injections, vision improved by 2 lines to 20/50+2, the hemorrhage resolved, and OCT showed no IRF/SRF. At that visit, the patient was treated with his fourth aflibercept injection, and treatment was extended to six weeks.

Dr. Mandelcorn is an assistant professor of ophthalmology at the University of Toronto. Dr. Alon is a retina fellow at the University Health Network (UHN) there. Dr. Brent is a clinician investigator at the Krembil Research Institute at UHN.

Disclosures: The authors have no relevant disclosures.

Focus on Retinal Imaging

GAINING NEW INSIGHTS INTO MACTEL

How the MacTel Project with multimodal imaging is expanding our knowledge of macular telangiectasia type 2.

Grant M. Comer, MD, MS

Macular telangiectasia (MacTel) type 2 is a slowly progressive, bilateral disorder of the pericentral maculae characterized by vascular and neuroglial retinal degeneration. Symptoms often start around the fifth decade of life and frequently include difficulty with reading due to missing letters within a word along with variable degrees of blurred and distorted central vision. Clinical findings are variable but may include perifoveal translucency, inner retinal crystals, non-tapering angled venules, intraretinal pigment, intraretinal atrophy, subfoveal yellow deposits, ectatic capillaries and subretinal neovascular complexes.

Multimodal imaging reveals a number of characteristic findings of MacTel. For example, fluorescein angiography, which has been the gold standard for diagnosis, illustrates telangiectatic capillaries early and hyperfluorescence consistent with leakage in the later phases (*Figure 1*), while blue light reflectance (ie, "red free") and autofluoresence, which are sensitive at detecting early disease, demonstrate characteristic hyper-reflective changes (*Figure 2, page 20*).[1]

In addition, spectral domain optical coherence tomography (SD-OCT) may reveal hyporeflective cavities (ie, cavitations) involving the inner and/or outer retinal lamellae and ellipsoid zone attenuation (*Figure 3, page 21*). Although the entire perifovea may be involved, the findings are nearly always observed in at least the temporal edge of the fovea and may be asymmetric between the eyes.

No treatments are effective at improving functional vision loss for the nonproliferative stage of MacTel type 2. However, intravitreous vascular endothelial growth factor (VEGF) inhibitors and, possibly, photodynamic therapy are often used to treat subretinal neovascularization and may improve visual acuity in the proliferative phase.[2]

MacTel Project Goals

Following J. Donald M. Gass, MD, and associates' initial descriptions of the disease decades ago, relatively few studies of macular telangiectasia type 2 have been published.[3,4] Therefore, the Macular Telangiectasia (MacTel) Project was established in 2005 as an international research collaboration to improve our understanding and, ultimately, find a treatment for this visually disabling disorder.

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Disclosure: The University of Michigan receives research support from the Lowy Medical Research Institute for participation in the MacTel Project clinical studies.

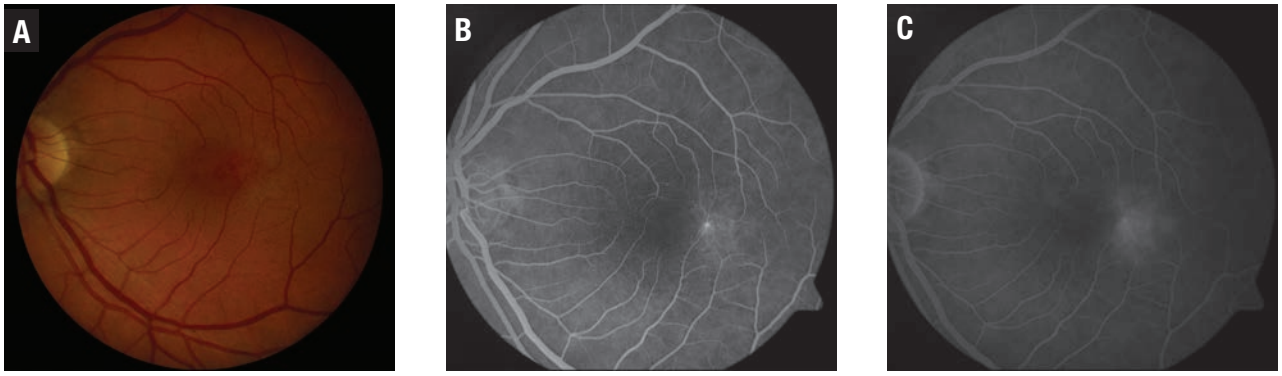

Figure 1. Color fundus photograph of the left eye (A) demonstrates non-tapering and angled venues, subtle perifoveal translucency and intraretinal crystals concentrated on the temporal edge of the fovea. Early phase fluorescein angiogram (FA) of the left eye (B) shows reduced and telangiectatic capillaries with subtle hyperfluorescence on the temporal edge of the fovea. Late-phase FA (C) demonstrates characteristic hyperfluorescence on the temporal edge of the fovea.

Organized into the three different programs—clinical research, eye donation and laboratory research—the MacTel Project is sponsored and coordinated by the private, not-for-profit Lowy Medical Research Institute (LMRI) based in La Jolla, Calif. Investigators around the world work independently and as part of multicenter studies to unravel the mysteries of macular telangiectasia type 2.

The clinical research program has evolved since its inception, but is currently divided into the Natural History Observational Registry Study, imaging and clinical trials groups.

Originally, the clinical research program consisted of only the MacTel Project Natural History Observational Study (NHOS), which eventually enrolled more than 550 participants and aimed to elucidate MacTel type 2-related changes longitudinally. Starting in late 2005, participants in the NHOS were evaluated annually for five years with visits that included a comprehensive history, ophthalmic examination and assessment of structural and functional measures.

Additionally, a parallel genetics study was initiated shortly thereafter in which blood samples were drawn from NHOS participants, first-degree family members and age-matched controls to identify genetic variants that may be associated with a susceptibility to MacTel type 2.

What NHOS Revealed About MacTel Type 2

As the largest study focusing on MacTel type 2, the NHOS provided important clinical information regarding baseline metrics and the natural history of the disease that include:

- mean age of 57 years at diagnosis;
- a predilection for female gender (64 percent) and Caucasian race (81 percent);
- mean Snellen visual acuity of approximately 20/32 in the better eye and 20/50 in the worse eye;
- 16 percent of participants demonstrated a 20/20 or better visual acuity an average of three years after diagnosis;
- hyperfluorescence on fluorescein angiography and characteristic autofluorescence changes in 89 percent of eyes;
- at least one MacTel type 2 specific change on OCT in 74 percent of participants;[5] and
- microperimetry revealed absolute scotomas in 43 percent of participants, with the temporal quadrant affected 98 percent of the time.[6]

MacTel type 2 was also associated with systemic disease. Patients demonstrated a higher prevalence of diabetes mellitus, elevated body-mass index, hypertension and history of cardiovascular disease than age- and sex-matched participants in population-based studies. Interestingly, the prevalence of diabetic retinopathy was significantly less than expected,

Take-home Point

The MacTel Project has transformed the understanding of macular telangiectasia type 2 since its inception in 2005. Investigators have better elucidated the clinical presentation and natural history, which allows for faster diagnosis and assists in counseling patients. Additional imaging modalities and pathological specimens have enabled a better understanding of the cellular mechanisms leading to disease. In addition, a Phase III clinical trial is set to begin within months that may offer the first hope of slowing the progression of the severe functional impairment. Finally, several genes have been identified that offer additional hope of halting or even reversing the deleterious effects of MacTel type 2. This new information will undoubtedly open a whole new line of inquiry in the quest to eliminate this visually disabling disorder.

which raised the possibility that MacTel type 2 was in some way protective against the development of diabetic retinopathy.[7]

After five years of follow-up, best-corrected visual acuity decreased by an average of 1.07 letters per year with 15 percent of participants losing more than 15 letters. In addition, the probability of progression from no crystalline deposits to any deposits, no intraretinal pigment to any pigment, and development of subretinal neovascularization was 20 percent, 33 percent and 7 percent, respectively.[8] Finally, enlargement of absolute scotomas on microperimetry was limited to an area of 5° by 8° regardless of the severity of the MacTel type 2.[6]

Importantly, the National Eye Institute Visual Function Questionnaire revealed significantly impaired visual function, even when the visual acuity was not proportionately affected.[9] Findings in a subcohort of 71 eyes followed for 4.5 years supported this, showing that functional deterioration was related more to absolute scotoma worsening on microperimetry (58 percent) than to a significant decline in visual acuity (17 percent).[10] Similarly, another study of 56 eyes followed for 4.5 years demonstrated a significant correlation between ellipsoid zone loss and absolute scotoma but not visual acuity. The authors suggested that ellipsoid zone changes might make an ideal surrogate for functional vision loss given the objectivity of the measure.[11]

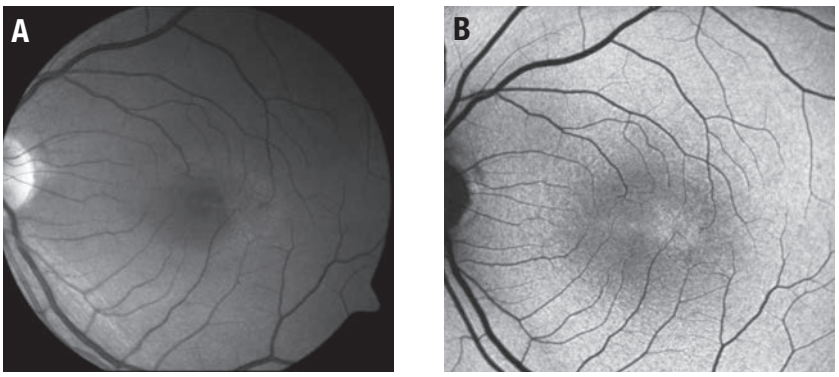

Figure 2. Blue light reflectance (ie, red free) image (A) shows hyper-reflectivity on the temporal edge of the fovea with a ring of subtle hyper-reflectivity throughout the perifovea. These images also illustrate the nontapering angled venules well. Fundus autofluorescence of the left eye (B) shows hyper-reflectivity on the fovea's temporal edge.

Natural History Observational Registry

The NHOS eventually transitioned into the Natural History Observational Registry, which is still enrolling patients. This registry is a means of identifying individuals who might be eligible for current and future MacTel Project studies in addition to gaining genetic information. In the registry, participants present to one of 21 participating sites within the United States, United Kingdom, Germany, Switzerland, France, Israel or Australia for an initial evaluation that includes a comprehensive history, ophthalmic examination and assessment of structural and functional measures in addition to a blood draw for genetic analysis. (*A list of participating sites is available at retina-specialist.com.*) Participants return to the referring ophthalmologist for long-term management. Sites contact patients yearly to keep their contact information current. More than 1,000 participants have enrolled so far.

MacTel Imaging Protocol

The Imaging groups supported by LMRI are using adaptive optics and OCT angiography to better understand the mechanisms of MacTel type 2 and develop an objective measure of disease progression.

Adaptive optics scanning laser ophthalmoscopy (AOSLO), which visualizes cone photoreceptor structure, has demonstrated disruption of the cone mosaic pattern in areas of the ellipsoid zone break on SD-OCT. This was thought to be permanent and progressive. However, a recent study using AOSLO microperimetry revealed that functioning cones are still present within these areas even though cones were not seen on AOSLO. Importantly, the AOSLO

Suggested Reading and Participating Sites

1. Issa PC, Gillies MC, Chew EY, et al. Macular telangiectasia type 2. Prog Retin Eye Res. 2013;34:49-77 (This publicly available review article consolidates the literature to offer a comprehensive description of MacTel as of 2013.)
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3. Official MacTel Project website: www.LMRI.net.

A list of clinical sites participating in the MacTel Project is available at retina-specialist.com.

has shown the ability to later visualize cones again in these areas as long as the external limiting membrane remains preserved, which suggests that some ellipsoid zone loss seen on SD-OCT may be reversible.[12]

OCT angiography (OCT-A) has revealed that capillary dilation and telangiectasis begins in the temporal perifoveal deep capillary plexus and extends to the superficial plexus before moving superficially around the fovea. More advanced MacTel type 2 demonstrates capillary thinning and ultimately loss of capillaries within these layers.[13] In some cases, neovascularization develops, which OCT-A has now shown affects both the retinal and choroidal layers rather than just the retinal and subretinal areas as previously believed.[14]

Clinical Trials

In collaboration with Neurotech Pharmaceuticals, the Lowy Medical Research Institute is sponsoring a clinical trials program to evaluate the safety and efficacy of ciliary neurotrophic factor (CNTF), a naturally occurring neuroprotective protein, against photoreceptor loss. Using encapsulated cell therapy (ECT) technology developed by Neurotech, the NT-501 device is surgically implanted into the vitreous where genetically engineered cells within a semi-permeable capsule release CNTF over an extended period.

An open-label Phase I clinical trial revealed no serious safety concerns in seven participants after four years.[15] A subsequent randomized, masked and controlled Phase II trial enrolled 67 patients (99 eyes) across 11 sites in the United States and Australia. The primary endpoint evaluated the effects of the NT-501 implant on the area of ellipsoid zone loss from baseline to month 24 as measured by en face imaging using SD-OCT. The area of loss increased by 0.213 mm^2 in sham-treated eyes compared to 0.148 mm^2 in CNTF treated eyes (p=0.03). In addition, secondary endpoints including the proportion of eyes with a 35 percent or more enlargement in ellipsoid zone loss from baseline (p=0.045) and maintenance of reading speed (p=0.016) favored the treated group over sham.[16]

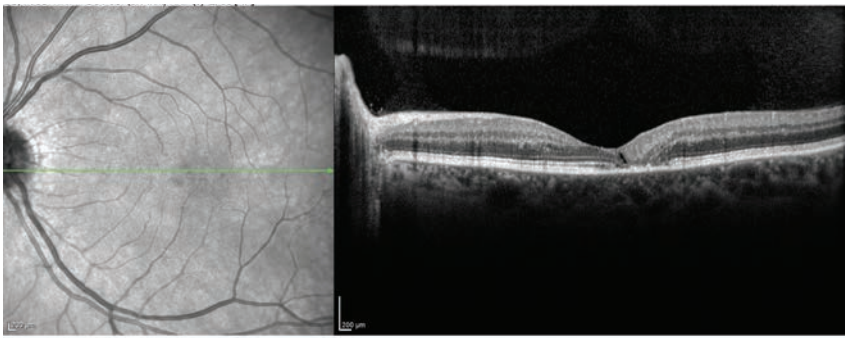

Figure 3. Horizontal spectral-domain optical coherence tomography of the left eye reveals a single cavitation through the middle layers of the retina with ablation of the ellipsoid zone just temporal to the central fovea.

A four-year extension study of the Phase I and II trials recently began and will consist of annual evaluations.[17] Additionally, a multicenter, masked, controlled Phase III clinical trial is anticipated to start by the end of 2017.[16] To participate in the Phase III clinical trial, prospective patients must first enroll in the Natural History Observational Registry study.

Eye Donation Program

The Eye Donation Program has allowed for the clinicopathological assessment of eyes with MacTel type 2 in order to gain a better understanding of the mechanisms of vision loss. Thus far, two cases have demonstrated an absence of Müller cell markers in the areas of macular pigment depletion. In addition, the second case found a significant loss of rods but not cones in the area of ellipsoid zone loss on SD-OCT.[18,19] Both cases involved fairly advanced MacTel type 2, and additional specimens are needed to better understand the histopathology. Details about the eye donation program are available on the LMRI website (www.lmri.net) or by contacting a MacTel project clinical site.

Laboratory Research

The Laboratory Research program aims to improve the understanding of MacTel through preclinical models and genetic analysis, and by identifying potential therapeutics.[20] It consists of extramural collaborators at institutions around the world and an intramural program based at the Lowy Medical Research Institute. The collaborators work independently and in concert to study the retina pigment epithelium, Müller glia, photoreceptors, metabolism, genetics, macular pigments, gene therapy and blood vessels. Additional information regarding the specific programs can be found on the LMRI website.

Recently, a genome-wide association study identified three validated susceptibility loci for MacTel type 2 on chromosomes 1p12, 2q34 and 5q14.3 in addition to two suggestive loci at 3q21.3 and 7p11.2. The 5q14.3 locus is associated with increased retinal vascular caliber while the 1p12,

(Continued on page 25)

Focus on Retinal Imaging

WHAT VASCULAR CHANGES MAY TELL US ABOUT MACULAR EDEMA AND DISEASE BURDEN

How quantitative assessment of perfusion and leakage dynamics may help direct management of retinal vascular disease.

By Jaya B. Kumar, MD, and Justis P. Ehlers, MD

Retinal ischemia can lead to devastating ocular complications including proliferative neovascularization, retinal detachment, glaucoma and subsequent poor visual outcome. Vascular endothelial growth factor (VEGF) is one of the identified growth factors that plays a key role in hypoxia-mediated retinal neovascularization. VEGF is an endothelial cell-specific angiogenic and vasopermeable factor that binds with high affinity to receptors with tyrosine kinase activity.[1–3]

Studies have demonstrated the presence of VEGF in fibrovascular membranes in eyes with diabetic retinopathy,[4] confirmed hypoxia stimulated secretion of VEGF in retinal pigment epithelium (RPE) cells,[5] and identified subsequent reduction in VEGF mRNA at a cellular level with normal oxygenation.[3] Retinal hypoxia contributes to the pathogenesis of diabetic macular edema (DME) and diabetic retinopathy (DR), and VEGF has been implicated as an important therapeutic target in DME and DR.[6,7] In addition, VEGF has been targeted in other retinal vascular diseases, such as retinal vein occlusive disease.[8–11]

The Anti-VEGF Effect

The introduction of novel VEGF antagonists has revolutionized the management of diabetic retinopathy with macular edema and retinal vein occlusion with macular edema.[12,13] Phase III trials of anti-VEGF therapy have demonstrated improved diabetic retinopathy scores, decreased macular edema, gain of visual acuity and reduced progression to neovascularization.[8,14,15] Aflibercept (Eylea, Regeneron Pharmaceuticals) showed greater than two-step improvement in Diabetic Retinopathy Severity Scale (DRSS) scores compared to laser, highlighting the role that anti-VEGF plays in regression of diabetic retinopathy.[14,16]

RISE and RIDE trials similarly showed patients treated with ranibizumab (Lucentis, Roche/Genentech) underwent significantly fewer laser procedures, and sustained improved visual acuity and diabetic macular edema.[17] The Diabetic Retinopathy Clinical Research Network (DRCR.net) revealed in Protocol T that all three anti-VEGF agents, including bevacizumab (Avastin, Roche/Genentech), ranibizumab and aflibercept were effective in treating DME, although some dif-

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ferences existed between the three drugs.[18]

In the VIBRANT study for branch retinal vein occlusion (BRVO), a direct comparison of laser treatment vs. anti-VEGF, demonstrated not only a greater reduction of macular edema in the anti-VEGF group but improved perfusion of the retina with less than 10 disc areas of capillary nonperfusion.[8] CRUISE (central retinal vein occlusion) and BRAVO (branch retinal vein occlusion) clinical trials demonstrated improved visual acuity and macular edema in the ranibizumab arms.[9,10] SCORE2 similarly showed that eyes treated with bevacizumab or aflibercept had improvement in visual acuity and macular edema in CRVO and hemiretinal vein occlusion.[11]

The COPERNICUS study for central retinal vein occlusion (CRVO) showed no progression to neovascularization in the VEGF trap-eye group compared to 7 percent in sham-treated eyes.[15] The authors postulated that anti-VEGF may allow reperfusion by inhibiting leukostasis and retinal ischemia triggered by VEGF. While many studies have demonstrated the efficacy of anti-VEGF in diabetic retinopathy and vein occlusion, the specific impact of anti-VEGF on retinal vascular dynamics, including vascular leakage, microaneurysms and ischemia, remains unclear.

The extent of peripheral retinal nonperfusion has been correlated with the severity of macular edema in diabetic retinopathy and vein occlusion. Michael A. Singer, MD, and colleagues found that eyes with increased peripheral nonperfusion had greater response to treatment with anti-VEGF, resulting in better visual acuity and decreased macular edema. Their study also suggested that eyes with macular edema are at higher risk of peripheral nonperfusion, underscoring the value of widefield angiography (*Figure 1*).[19] While this study looked at qualitative changes in angiogram, few reports have demonstrated quantitative improvements with ischemia following anti-VEGF therapy.

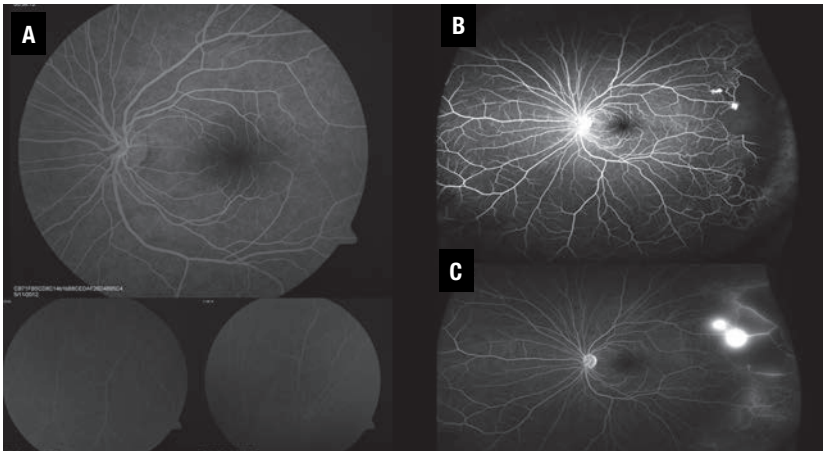

Figure 1. Regular fluorescein angiography (FA) (A) did not show the peripheral nonperfusion and neovascularization highlighted on widefield FA (B, C).

Tools for Evaluating Angiographic Findings

Objective and quantitative measurement tools for angiographic features have been lacking. Current analysis is limited to the clinician's subjective interpretation. Various investigators have described potential approaches to quantitative assessment of angiographic and widefield angiographic features. Colin Tan, MD, and colleagues in Singapore used stereographic projection software to correct for peripheral distortion and calculate areas of ischemia in anatomically correct physical units (mm^2).[20] Hossein Rabbani, MD, and colleagues created an automated algorithm that reproducibly detected areas of leakage on fluorescein angiograms in diabetic macular edema.[21] Yonatan Serlin, MD, and colleagues in Israel presented a new method to quantify retinal vascular permeability in diabetic retinopathy.[22] We recently presented an automated software platform that quantifies microaneurysms and leakage segmentation in ultra-widefield angiograms (*Figures 2 and 3, page 24*).[23]

Quantitative assessment can provide unique opportunities for understanding underlying changes in retinal vascular dynamics. Moreover, objective measurements will likely play a pivotal role in tracking patients' progression and response to treatment.

Studies are under way focusing on objective analysis of angiographic

Take-home Point

Quantitative assessment of perfusion and leakage dynamics in macular edema, whether due to diabetic retinopathy or retinal vein occlusion, can provide retina specialists with unique opportunities to understand the underlying pathology. Gaining a better understanding of these vascular changes and being able to obtain objective measurements may play an important role in monitoring disease progression and treatment response.

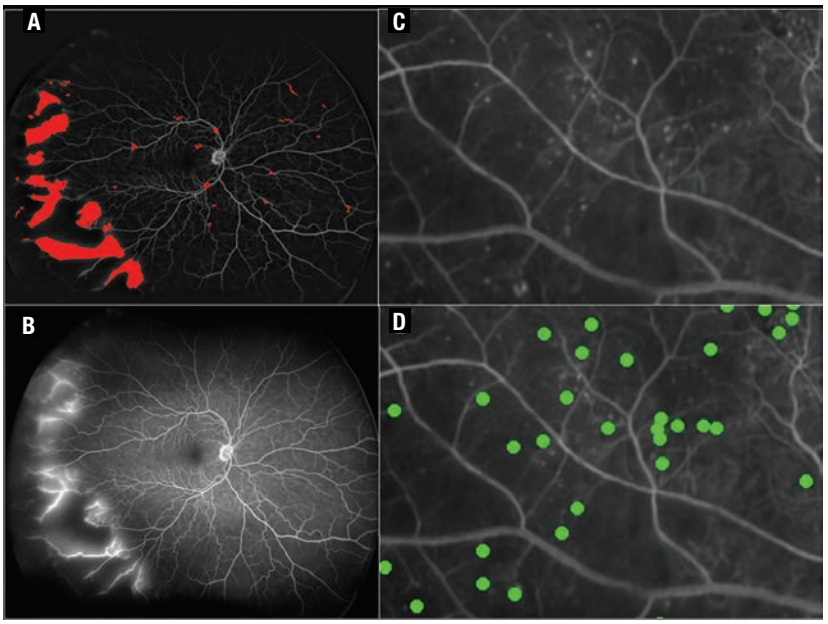

Figure 2. Examples of quantification of leakage segmentation in red (A,B) and microaneurysms (C, D) shown in green in diabetic retinopathy.

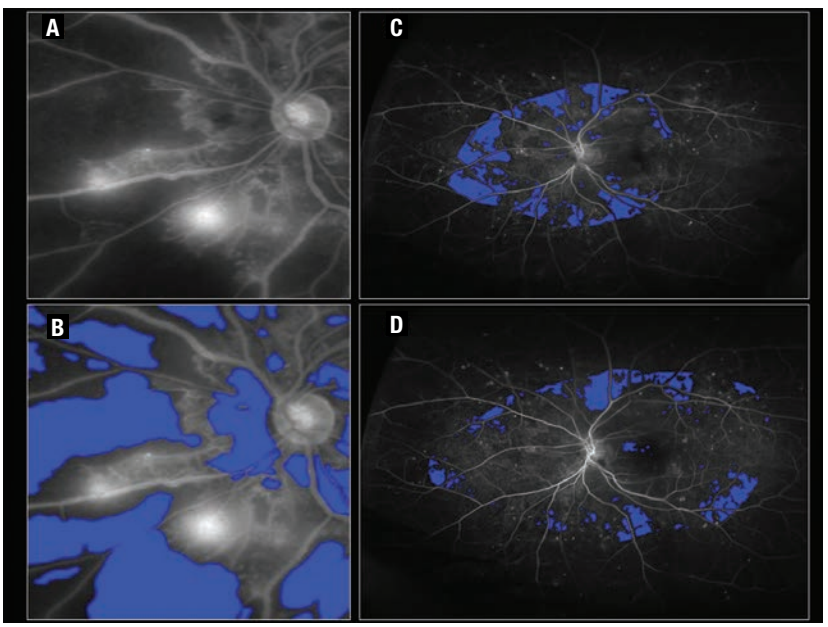

Figure 3. Examples of ischemia segmentation seen in blue (A,B), at baseline (C) and at one year (D) in diabetic retinopathy.

parameters in diabetic retinopathy. PERMEATE is an ongoing clinical trial investigating retinal vascular dynamics with a novel angiographic quantitative assessment tool in eyes with DME or retinal vein occlusion treated with intravitreal aflibercept. Preliminary six-month data showed study eyes treated with intravitreal aflibercept had improvement in visual acuity, decrease in the number of microaneurysms, less leakage and smaller areas of ischemia.[24] Final results will be available soon. The REACT study is a recently completed study that is also investigating quantitative assessment of widefield angiography in eyes with treatment-resistant diabetic macular edema that were converted from bevacizumab to ranibizumab (*ClinicalTrials.gov: NCT01982435*).

Seeking Metrics for Following Diabetic Retinopathy

Because multiple therapeutics are undergoing evaluation as potential agents to treat diabetic retinopathy, clinicians need objective metrics to monitor treatment response. Ranibizumab recently received approval for diabetic retinopathy without macular edema based on DRCR.net Protocol S results.[25] Patients with proliferative diabetic retinopathy were randomized to panretinal photocoagulation or 0.5-mg ranibizumab intravitreal injections. The ranibizumab group with and without diabetic macular edema had improvement in diabetic retinopathy severity scale.

Another trial, PANORAMA, is assessing the efficacy of aflibercept for improvement of moderately severe to severe nonproliferative diabetic retinopathy (*ClinicalTrials.gov: NCT02718326*). Promising results from the TIME-2 study group demonstrated that AKB-9778 Tie2 activator (Aerpio Pharmaceuticals) combined with ranibizumab resulted in decreased diabetic macular edema compared to VEGF alone.[26] Aerpio has reported that AKB-9778 is in a Phase IIb clinical trial to assess its role in stabilizing blood vessels to prevent vascular leakage and angiogenesis in diabetic retinopathy.

With the advent of intravitreal

injections to treat diabetic retinopathy without macular edema, what are the metrics to follow these patients? What objective features can the clinician rely on? While optical coherence tomography (OCT) is indispensable to our decision making in managing macular edema, we need another tool to serve as a barometer in decision making for diabetic retinopathy and vein occlusion.

Although widespread availability of objective quantitative assessment of angiographic features is currently lacking, new and emerging technologies hold significant promise to enable objective measures of retinal vascular disease severity. Quantification and automated segmentation would allow for rapid and objective assessments of numerous disease features, including alterations in disease activity, pattern-based automated disease recognition or stratification, and individualized therapeutic decision making based on features and integrative pattern analysis. Additional research is needed to better understand the role for quantitative angiography for ongoing management of retinal vascular disease and for the potential impact on future clinical trial endpoints.

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Gaining New Insights Into MacTEL

(Continued from page 21)

2q34 and 7q11.2 loci play a role in the glycine and serine metabolic pathway. Interestingly, a metabolomics analysis demonstrated significantly reduced blood serum glycine (p=4.04x10-6) and serine (p=2.48x10-4) levels for MacTel type 2 cases vs. controls.[21]

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Focus on Retina Surgery

Triamcinolone Acetonide Assist For ILM Peeling During RRD Repair

This peeling approach during vitrectomy for rhegmatogenous retinal detachment can prevent post-surgical epiretinal membrane growth.

By Kunihiko Akiyama, MD

Epiretinal membrane (ERM) growth is not a rare complication after surgical repair of rhegmatogenous retinal detachment (RRD), and it may cause severe visual loss or metamorphopsia. Such symptomatic ERMs usually develop suddenly within several months after vitrectomy for RRD repair (*Figure 1A*).[1,2] Here, I describe a technique to prevent ERM growth that uses triamcinolone acetonide for internal limiting membrane (ILM) peeling.

The prevalence of a post-surgical ERM has been reported to be from 4.4 to 16 percent,[3–5] and as high as 34.4 percent in a certain condition.[6] Surgical removal of the ERM is effective in retaining or recovering vision of patients with post-surgical ERMs.[7]

However, the visual prognosis after ERM removal may not be good, especially for patients who had been treated for macula-sparing RRDs, which are not expected to cause visual impairment when treated successfully. A previous study reported that mean Snellen visual acuity was 20/40 after subsequent vitrectomy to remove an ERM that developed after repair of macula-sparing RRD.[8] We recently reported that final visual acuity of 20/20 or better was achieved in only three of seven cases after removal of symptomatic post-surgical ERMs secondary to macula-sparing RRD.[2]

Another possible consequence of removal of ERMs is persistent metamorphopsia. Taking these facts into consideration, prevention of post-surgical ERM is desirable as long as it is achieved via a safe and practical procedure.

Pathogenesis of ERM

ILM peeling has been known to prevent post-surgical ERM growth in complicated RRD cases accompanied by proliferative vitreoretinopathy (PVR), silicone oil tamponade or diabetic retinopathy.[9-11] Recently, ILM peeling has also been advocated as a procedure to prevent recurrence of ERMs after surgical removal of idiopathic ERMs.[12]

Authors have proposed that pathogenesis of ERMs is in association with residual vitreous cortex[13] and remnant cell components,[14,15] both of which are observed on the ILM surface. Histopathologically, various types of cells have been proven to exist in ERMs.[15] While controversy surrounds the difference in cell distribution between idiopathic ERMs and other types of secondary ERMs or PVR membranes,[14,15] authors have assumed that post-RRD ERMs comprised of retinal pigment epithelial (RPE) cells leak into the vitreous cavity through a retinal tear.[14,16] In the process of the proliferation and

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migration of those cells that grow into ERMs, an ILM is as important as a scaffold. Therefore, strategies to prevent ERM arise from removal of these previously mentioned mechanisms of ERM proliferation:

- residual vitreous cortex;
- cell components; and
- a scaffold for cellular proliferation.

Triamcinolone acetonide staining can facilitate complete removal of vitreous cortex,[13] whereas the other two factors still remain unsolved. In fact, ERM growth has sometimes been confirmed after RRD repair in which complete removal of vitreous cortex has been ensured using TA.[1,2] For further prevention of post-surgical ERM growth by eliminating cell components and the scaffold itself, some investigators have suggested using ILM peeling.[1,2,6]

How Efficacious Is ILM Peeling?

In a retrospective review of 102 consecutive cases that underwent initial vitrectomy for RRDs and were observed for at least six months postoperatively, we reported a significant preventive effect of ILM peeling on post-surgical ERM development.[2] ILM was peeled with or without the assistance of TA staining (*Video available at bitly.ly/RS_ILM_004*). We did not use indocyanine green because of its potential to damage macular function.

Of the 102 cases in our study, 58 were treated with ILM peeling and 44 without. We confirmed ERM growth in 21 cases treated without ILM peeling, and observed no ERM growth in any cases with ILM peeling ($p<0.001$). Ten of the 21 cases had severe ERM growth that caused significant visual loss ≥ 0.2

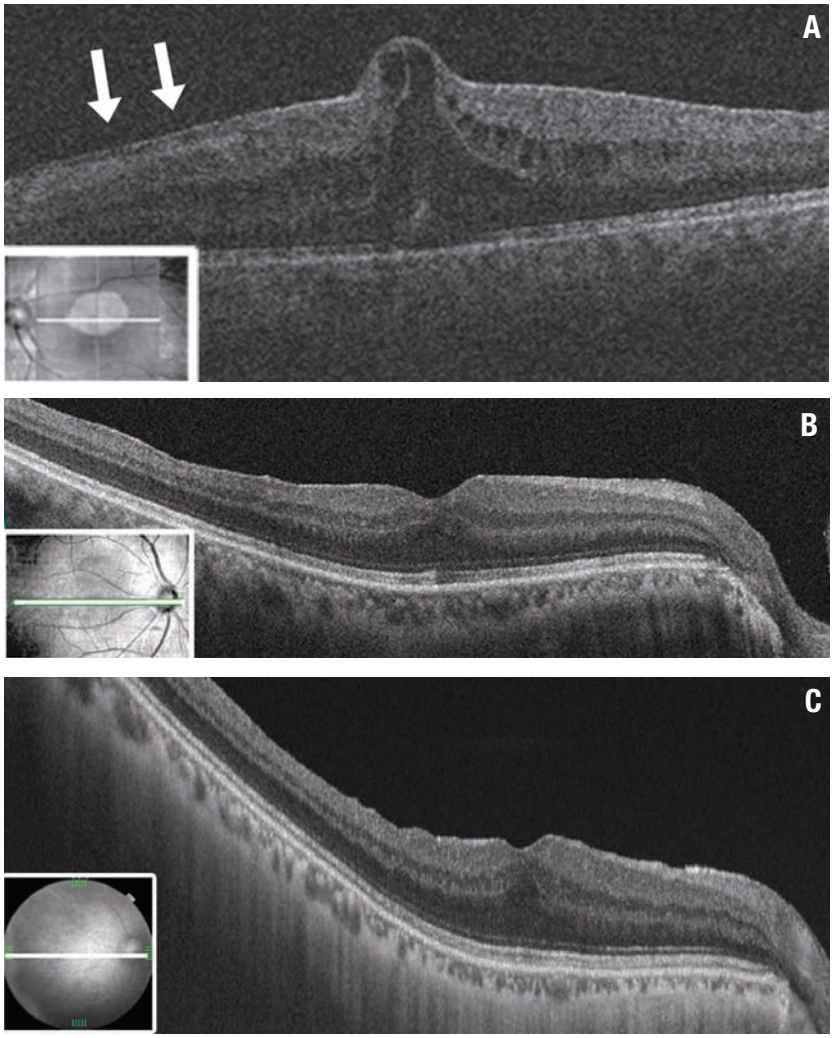


Figure 1. Optical coherence tomography (OCT) shows severe epiretinal membrane (ERM) growth after vitrectomy for bilateral macula-on rhegmatogenous retinal detachment (RRD) repair in a 58-year-old man. The left eye was treated using a conventional method without internal limiting membrane (ILM) peeling. A severe epiretinal membrane developed suddenly two months later (A), which required surgical removal because visual acuity had dropped to 0.5 (20/40). Subsequently the right eye, treated with ILM peeling showed no ERM growth for more than three years and retained best-corrected visual acuity of 1.2 (≈20/16). OCT scans show the right eye at one month (B) and three years (C) postoperatively. These images present similar configurations in terms of the thickness and integrity of each layer, except for the presence of retinal dimpling at three years. (*Figure 1A used with permission Elsevier: American Journal of Ophthalmology*)

Take-home Point

Prevention of epiretinal membrane (ERM) growth after rhegmatogenous retinal detachment (RRD) repair is desirable because the condition may cause persistent visual impairment even after surgical removal. Internal limiting membrane (ILM) peeling prevents ERM growth effectively, with favorable visual outcomes without severe complications. Wrinkling of the ILM surface might be considered to be a sign of a primitive form of ERM growth and may be a marker that a patient would benefit from ILM peeling.

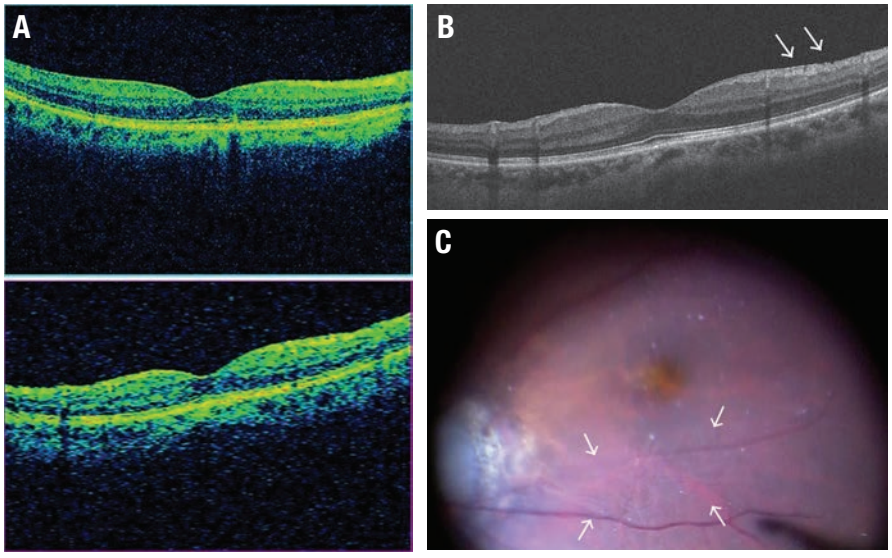


Figure 2. Preoperative optical coherence tomography images and an intraoperative view of a patient with macula-sparing rhegmatogenous retinal detachment in the right eye show wrinkling of the inner surface of the macula, which looks normal on the cube protocol OCT scan (A), whereas a thin membrane with fine folds (arrows) is present on the five-line raster protocol vertical scan representing a primitive form of an epiretinal membrane (ERM) (B). The photo captured from intraoperative observation using a meniscus contact lens shows fine wrinkling on the surface of the ILM (C, surrounded by arrows). In this case, the wrinkling and the primitive ERM formation can be observed rather distinctly, but there are many cases in which the wrinkling is too fine to be captured by OCT scan or observed by a wide-viewing operating system. In order to avoid missing such findings that might later progress to ERM growth, precise observation under appropriate magnification is essential.

logMAR (logarithm of the minimum angle of resolution) compared to the highest visual acuity obtained before detection of ERM. Nine of these cases (8.8 percent of all total cases and 20.4 percent of ILM-not-peeled cases) underwent a subsequent surgery to remove the post-surgical ERMs.

The prevalence of severe ERM growth was also significantly higher in cases without ILM peeling ($p<0.001$, not discussed in this article). Thus, our results strongly indicate that ILM peeling is efficacious in preventing post-RRD ERM growth, either in terms of severe ERMs (10 cases) or any ERMs (21 cases) including asymptomatic ones.

Safety of ILM Peeling

In our study, best-corrected visual acuities of cases treated with ILM peeling were not inferior to those of cases without ILM peeling, either at baseline or at the final examination.[2] Other investigators have reported similar results.[1,6]

Additionally, we conducted further analyses of the visual prognosis after vitrectomy for macula-sparing RRDs to evaluate the influence of ILM peeling on the normal fovea. We confirmed final visual outcomes of 40 patients treated with ILM peeling with the mean (±SD) postoperative BCVA of -0.05 ±0.06 (in logMAR), which was better than 20/20.[17]

Our study found no severe complications related to ILM peeling such as an iatrogenic retinal break in the macula, a macular hole (MH) or submacular hemorrhage. Although we observed in many of our cases a well-known morphologic change after ILM peeling, dissociated optic nerve fiber layer (DONFL) appearance or inner retinal dimpling (*Figure 1C, page 27*), it did not lead to a decline of post-surgical BCVA, which is in line with previous reports.[18, 19] ILM peeling is unlikely to cause severe complications or adverse impact on post-surgical vision.

ERM Growth MH Formation After RRD repair

A macular hole is a rare but vision-threatening complication after RRD repair. Although the pathogenesis of post-surgical MH formation is still unclear, a recent report has suggested a relationship between post-RRD MH formation and ERM growth.[20] In this regard, ILM peeling could prevent MH formation as well as ERM growth after vitrectomy for RRD.

ERM growth, which has been proposed to cause tangential traction at the fovea, is usually detected by its typical appearance on slit lamp examination and confirmed on optical coherence tomography (OCT) images.

However, an ERM (or thickened residual vitreous cortex) could occasionally exist where neither OCT nor a slit lamp exam reveals its presence ; it may only be identified during vitrectomy to repair secondary MH. This suggests that ERM growth may be more common after RRD repair than we thought based on observation using OCT scans. Clinically, undetectable ERMs usually remain harmless and do not require surgical intervention, whereas they could potentially play an important role in the pathogenesis of post-surgical MH formation.

Who Will Benefit From ILM Peeling?

Our data imply that ILM peeling could be considered as a prophylaxis for ERM development for any patient undergoing vitrectomy for RRD, unless the surgeon notes some unfavorable conditions. These include:

- instability of the patient's eye or head;
- poor intraoperative visibility; or
- extreme fragility of the retina.

However, controversies remain with regard to the technical difficulty of this procedure. When comparing common RRD to MHRD and foveal schisis associated with pathological myopia, both of which are familiar to vitreoretinal surgeons, ILM peeling in macula-involving RRD is generally easier than in MHRD. In macula-sparing cases, ILM peeling is much easier than in foveal schisis.

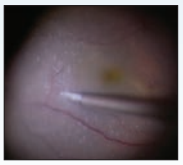
On the other hand, one cannot completely exclude the potential adverse effect of ILM peeling on long-term visual outcomes after several decades, as several investigators have discussed in association with morphological alterations.[19, 21–23] To avoid this potential risk, surgeons can apply ILM peeling to selected cases that are more likely to develop an ERM. Although some investigators have tried to identify the risk factors for ERM growth in terms of the extension of RRD, types and location of retinal tears and macular involvement, they have yet to reach a consensus.

Surface wrinkling retinopathy is a term used to describe the wrinkling of the inner retinal surface that is accompanied by ERM.[24] Similar wrinkling is sometimes detected on the macula by careful observation using a meniscus contact lens during vitrectomy for RRDs (*Figure 2*).

No evidence exists so far to relate this finding to subsequent ERM growth, but wrinkling could represent its earliest sign, provided that "surface wrinkling is never seen without an epiretinal membrane," as Albert M. Roth, MD, and Robert Y. Foos, MD, reported in the 1970s before OCT was available.[24] Then, ILM peeling may have been most beneficial for eyes having this phenomenon. Currently, we are peeling ILM in selected cases based on the presence of this early sign, although the number of cases is not large enough to draw a conclusion.

We should note that surface wrinkling is not always detected by OCT scans (*Figure 2*). Therefore, appropriate magnification and resolution is essential in order to observe the macula meticulously during vitrectomy, lest it go undetected. RS

View the Video



Watch as Dr. Akiyama demonstrates techniques for triamcinolone acetonide-assisted internal limiting membrane peeling on a detached macula. Available at: bitly.ly/RS_ILM_004.

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Focus on Retina Surgery

STEM-CELL THERAPY FOR NON-nAMD: WE'RE GETTING CLOSER

A look at advances in stem-cell biology, regenerative medicine, non-invasive retinal imaging and vitreoretinal surgery.

By Tai-Chi Lin, MD, Tony Succar, MScMed (OphthSc), PhD, Kaitlin Kogachi and Amir H. Kashani, MD, PhD

Many outer retinal degenerative diseases such as retinitis pigmentosa, age-related macular degeneration and Stargardt disease share a common endpoint of photoreceptor and retinal pigment epithelium (RPE) loss that leads to severe vision loss. RPE replacement strategies may be feasible for many of these diseases, but AMD is the subject of particular interest because of its prevalence. In this article, we focus on AMD, recognizing that many stem-cell therapy advances for AMD may translate to other degenerative retinal diseases.

Anti-VEGF therapy has been very effective in disrupting the progression of neovascular AMD (nAMD) and even reversing vision loss in many cases. However, non-nAMD, characterized by regions of irreversible RPE cell loss, or geographic atrophy (GA), slowly results in severe and irreversible vision loss. The Age-Related Eye Disease Study (AREDS) showed progression from intermediate to non-nAMD takes about 2.5 to five years.[1] To date, no effective treatment exists for non-nAMD.

The exact etiology of AMD is unknown, but a combination of genetic and environmental factors have been implicated.[2,3] While the primary cause of acute vision loss in nAMD is choroidal neovascularization (CNV), RPE loss and geographic atrophy are final common endpoints for both nAMD and non-nAMD.

Questions Stem Cell-based Therapy Must Answer

The RPE monolayer is essential both for the survival of photoreceptors and the underlying choriocapillaris. Among other functions, the RPE secretes pigment epithelial-derived factor (PEDF), vascular endothelial growth factor (VEGF) as well as the extracellular matrix which may have an antiangiogenic function.

For this reason, any stem cell-based therapy must answer several questions, among them:

- Will the donor RPE survive long enough to justify surgical risks?
- Will the donor RPE maintain its polarity and function; that is, will donor RPE form functional synaptic connections with host photoreceptor neurons and facilitate the visual cycle?
- Can the donor RPE reverse or prevent further degeneration?

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- Are sources of donor RPE ethically available?
- What is the best surgical technique?

While RPE replacement strategies are not likely to benefit the acute vision loss associated with CNV in nAMD, the prevalence of GA as a final common endpoint in both nAMD and non-nAMD suggests that both forms of the disease may benefit from RPE replacement strategies at some point.

Investigators demonstrated proof-of-principle decades ago that RPE transplantation could work in human subjects and animal models.[4–6] These studies were complemented by macular surgeries that demonstrated that translocating the fovea over an apparently normal region of RPE allowed short-term visual gains.[7] Unfortunately, long-term follow-up showed high GA recurrence rates in the new subfoveal RPE region.[8,9]

Other sources of cells have been used as donor RPE including homologous, heterologous or autologous adult RPE transplantation as well as fetal RPE transplantation.[8,10-14] Attempts at human RPE transplantation in GA using autologous and allogeneic RPE have had limited success but strongly suggest that RPE replacement strategies can work if the limitations associated with the cell sources and surgical methods could be overcome.[15-20]

Focus for the Future Of Stem Cell Research

- Development of novel, noninvasive diagnostic tests to assay retinal pigment epithelium and retinal function at the molecular and cellular level.
- Development of novel surgical tools and surgical methods for optimal delivery of RPE.
- Advancement of stem-cell science for the purpose of understanding host retinal immune response.
- Development of clinical-grade methods to genetically modify stem cell-derived RPE.
- Development of rehabilitation strategies for training patients to use optimum fixation viewing techniques with transplanted stem cells for visually guided tasks to enhance function.

Sources for Stem Cells

Investigators have reported several hundred RPE or stem cell-based grafts since the first human homologous and autologous RPE transplantation in 1991, and this number is growing.[16,21,22] Some of these studies use non-RPE stem-cell populations, such as bone marrow-derived stem cells, delivered with either intravitreal or intravenous adminstration.[23] The predominant mechanism of action of these studies is through nonspecific trophic effects of stem cells to support retinal and RPE function. Interestingly, evidence has shown RPE repopulation by systemic administration of some bone marrow-derived cell lines in animal models,[24,25] but the safety and efficacy of systemic administration seems more problematic than with local delivery methods, which are also viable and very well developed.

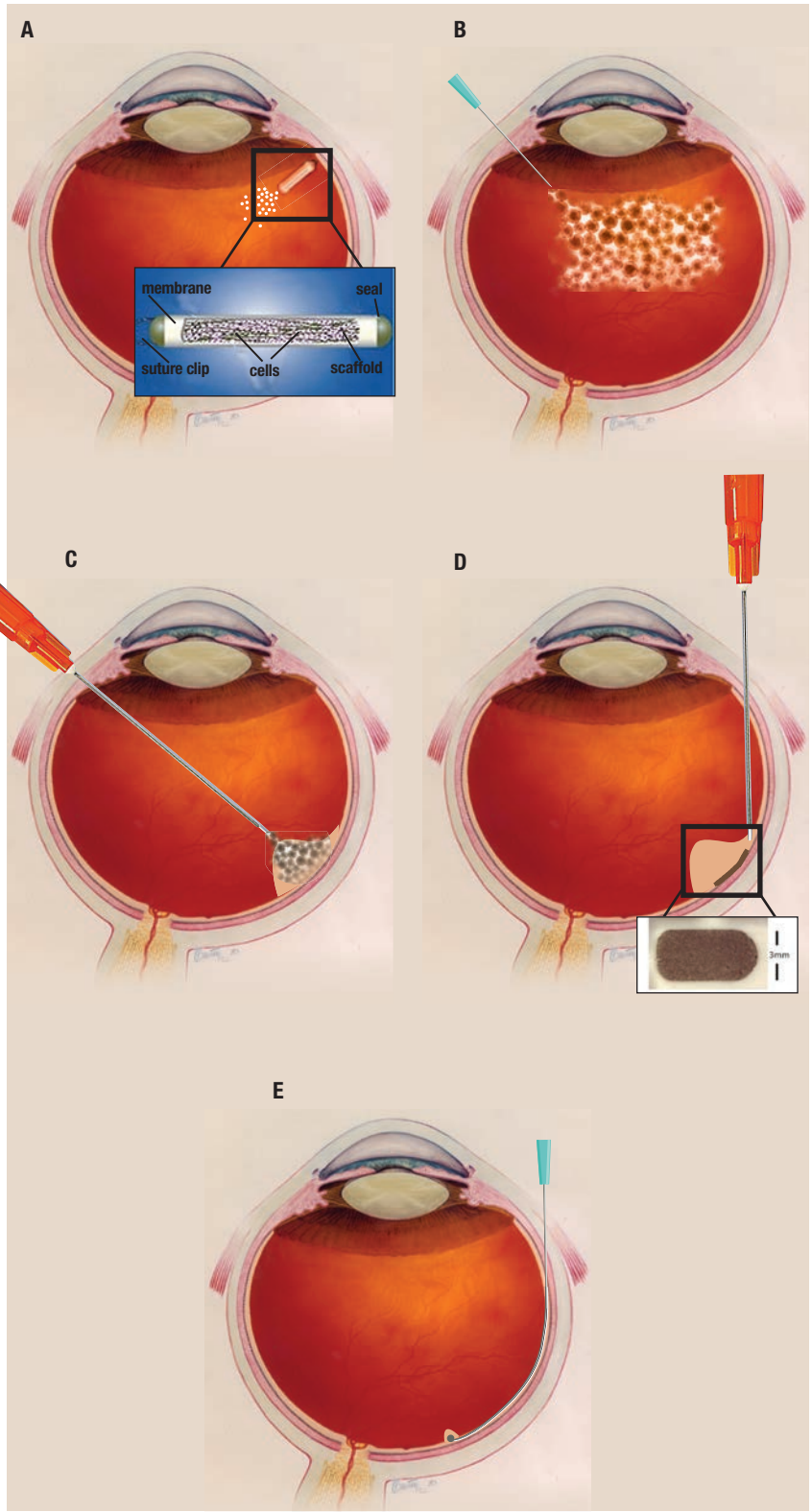
Among the numerous sources of donor RPE, induced pluripotent stem cells (iPSC) and human embryonic stem cells (hESC) are the most feasible. Both stem cell forms are a source of potentially endless RPE donor cells that can be fully differentiated into RPE either as cell suspension or monolayers.

• ***iPSC.*** Induced pluripotent stem cells are derived from fully differentiated adult somatic cells that are reprogrammed *in vitro* to differentiate into RPE.[25] They perform phagocytic functions, demonstrate RPE-like gene expression profiles and promote photoreceptor survival.[26–28] A Japanese study that used autologous iPSC RPE cells for AMD therapy was recently stopped due to unexpected mutations (three aberrations in DNA copy number),[27,29] and was suspended because of concerns about the possible effects the deletions could have.[30,31]

• ***hESC.*** In contrast, human embryonic stem cells are derived from the inner cell mass of blastocysts and can also be programmed to differentiate into RPE.[31] Manufacture of these cells can undergo strict quality-control testing and avoid the complicated and high-risk process of

Take-home Point

The quest to restore sight from several blinding retinal diseases has shown promise through groundbreaking research emerging from stem cell-based therapies. Subretinal transplantation of autologous or allogeneic retinal pigment epithelium (RPE) over the past several decades has shown that stem cell-derived RPE can rescue photoreceptor function and improve some aspects of visual function in animal models and in human subjects with neovascular age-related macular degeneration and non-neovascular AMD. Thanks to advances in stem-cell biology and regenerative medicine, new methods of differentiating RPE from human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC) can provide a potentially unlimited supply of RPE cells. Parallel advances in noninvasive retinal imaging and vitreoretinal surgery now provide the tools to effectively identify relevant anatomic changes with functional correlations ***in vivo*** and deliver stem cell-based therapies. This review focuses on the potential and challenges of stem cell-based treatments for AMD.



surgically harvesting autologous or allogeneic grafts.

Lastly, both hESC and iPSC may be amenable to genetic manipulation. This may allow manipulation of immunogenic properties or introduction of new genes to supplement function of the cells *in vivo*.

Regardless of the stem cell source, transplanted RPE cells will likely require some form of mechanical or physical substrate because RPE survival depends highly on extracellular substrates.[32,33] For example, a healthy Bruch's membrane has been shown to improve the survival, repopulation and confluence of RPE cells.[34]

Such a substrate must not only support RPE attachment and differentiation; it must also be amenable to surgical manipulation and be immunologically silent. While donor RPE in suspension may attach to exogenous Bruch's membrane, they more commonly aggregate in multiple layers and assume an abnormal phenotype.[35]

In addition, dissociated hESC-derived RPE can dedifferentiate and may not redifferentiate appropriately. Groups have developed various scaffolds to support RPE survival and implantation, including biodegradable scaffolds and biologically inert but nondegradable scaffolds such as polyester membranes, plasma polymers, polyimide and parylene.[20,36–39] Researchers have shown that subretinal implantation of human embryonic stem cell-derived RPE mono-

Figure. Methods for delivering stem cells include: A) intraocular encapsulated cell technology via insert; B) intravitreal injection; C) pars plana vitrectomy with subretinal cell suspension injection via cannula; D) pars plana vitrectomy with subretinal graft placement via cannula; and E) subretinal delivery of stem-cell suspension.

layers on a parylene substrate have improved survival compared to cell suspensions.[40,41]

Evaluating the Host Tissue

Detailed assessment coupling macular anatomical and functional correlations are critical for assessing the viability of a subject's retina for stem cell-based rehabilitation and for postoperative assessment of success.

Spectral-domain optical coherence tomography (SD-OCT) allows detailed assessment of photoreceptor structure and has shown that not all regions of GA are uniform.[40,42] Autologous RPE transplantation suggests that subjects with recent loss of visual function may benefit most from RPE transplantation.[43] It seems that the visual potential of neurosensory retina over areas of long-standing GA is poor.

Subjects with such severe and chronic anatomical changes may not show significant improvement in visual function under any circumstances. It is possible that RPE transplantation in this population may preserve the remaining RPE and retina at the borders of geographic atrophy lesions or slow the progression of disease.

It is exciting to speculate about stem-cell therapy as a replacement for neurosensory retina, specifically photoreceptor cells, either alone or in addition to RPE transplantation, although this is not currently in any clinical trial. Since most cases of severe non-nAMD ultimately involve loss of photoreceptors, it is likely that such a treatment will be necessary for severe disease.

Interestingly, transplantation of human fetal retina into nude adult rat retina has resulted in histologically detectable synaptic connections.[44] Adult retinal transplantation in humans has been demonstrated to be safe in subjects with end-stage retinitis pigmentosa and AMD, but gains in visual function have not been demonstrated.[45–48]

Recent Clinical Trials Of Stem Cells for AMD

A number of recent clinical trials have been very promising in demonstrating the safety of stem cell-based therapies and their potential for improved visual acuity. Here we discuss three of them.

Researchers at the RIKEN Center for Developmental Biology and the Center for iPS Cell Research and Application in Japan assessed the feasibility of transplanting a sheet of RPE cells, differentiated from induced pluripotent stem cells (iPSCs), in a 77-year-old woman with advanced nAMD and polypoidal choroidal vasculopathy.[31] The iPSCs were differentiated and generated from the patient's skin fibroblasts.

This patient did not receive immunosuppressants and showed no signs of rejection. Furthermore, no serious adverse events were noted at 25 months of follow-up. Optical coherence tomography images indicated good retinal integrity over the graft at one year. The patient also noted improvement in iPSC-based Visual Functioning Questionnaire-25 score, a secondary outcome, and expressed satisfaction with "brighter" vision, which was probably due to removal of the neovascular membrane. After one year, the patient's best-corrected visual acuity had neither improved nor decreased, although the transplanted sheet remained intact with cystoid macular edema.

Advanced Cell Technologies and investigators at UCLA conducted a longitudinal prospective clinical study at four years follow-up to establish the safety and tolerability of subretinal transplantation of human embryonic stem cell-derived RPE in patients with either Stargardt disease or non-neovascular AMD.[54] In the nine patients with non-nAMD, most showed improvement in best-corrected visual acuity (BCVA) at both six and 12 months, and the rest remained stable.

Among the Stargardt patients, most remained stable at six and 12 months, and while a few showed improvement, one patient's vision worsened at both intervals. The authors found 13 of 18 patients (72 percent) demonstrated increased subretinal pigment after transplantation at the border of the atrophic area. Some of these areas were found to demonstrate reconstitution or thickening of the RPE layer on OCT, possibly suggestive of successful cellular engraftment. However, the authors noted that these anatomic outcomes cannot be definitively ascribed to the transplanted cells in the absence of higher-resolution imaging techniques, microperimetry or any specific label for the transplanted cells.

Researchers from Wills Eye Hospital and Janssen reported on the safety, tolerability and clinical response to a single subretinal dose of human umbilical tissue-derived cells (palucorcel [CNTO-2476]) in patients age 50 years and older.[55] They administered palucorcel in 33 eyes in a Phase I/IIA multicenter, open-label, dose-escalation, fellow eye-controlled study. Overall, 17.1 percent of subjects experienced retinal detachments and 37.1 percent experienced retinal perforations. They observed no episodes of immune rejection or tumor formation. At year one, they observed ≥10- and ≥ 15-letter gains in BCVA in 34.5 percent and 24.1 percent of eyes receiving palucorcel, respectively, and in 3.3 percent (for both) of fellow eyes.

They concluded that the subretinal delivery procedure was associated with a high rate of retinal perforations and retinal detachments so future studies would require a modified surgical approach. When cells were sequestered in the subretinal space, palucorcel was well tolerated and may be associated with improvements in visual acuity. Larger randomized controlled studies are required to confirm these results.

Stem-Cell Delivery Techniques

Regardless of the source of RPE, the delivery techniques include intravitreal injection, subretinal injection of cell suspension of RPE or subretinal placement of a sheet of

tissue containing RPE (*Figure D, page 32*).[49]

Injection of cell suspensions into the subretinal space is advantageous because it does not require a large retinotomy and is relatively fast and simple.[50] Major limitations of this method include the reflux of RPE cells into the vitreous, relatively poor adherence to Bruch's membrane and failure to form an effective monolayer.[36,51]

Alternatively, the delivery of subretinal sheets containing RPE has also been demonstrated but requires larger retinotomies, takes longer and is prone to incorrect implant orientation and more postoperative complications.[36,52]

The main advantage of implanting RPE sheets with a scaffold is that the orientation, polarization and function of the RPE is more likely to consistently replicate that of the native RPE.

Despite the limitations of both methods, current clinical trials hold some promise.[22,44,52,53] In some cases cells can be implanted in a self-contained and nonimmunogenic manner that allows the secretion of trophic factors but isolates the cells from the host environment. RS

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A Look at Our Phase I/IIA Trial of hESC-derived RPE

A great deal of evidence suggests that retinal pigment epithelium transplantation can restore at least some aspects of retinal structure, function and vision in animals and humans with age-related macular degeneration. Advances in cell biology, surgery, retinal imaging, and physiology have enabled several human clinical trials that may offer vision-restoring therapy to millions of people affected by non-neovascular AMD. Early phase human clinical trials are in progress and the results are highly anticipated.

Our group at the University of Southern California, in collaboration with researchers from the University of California Santa Barbara, the California Institute of Technology and the City of Hope, is conducting a Phase I/IIA clinical trial of human embryonic stem cell-derived RPE supported by a parylene substrate that mimics native Bruch's membrane. The study is currently ongoing and it is too early to report results but continued research and collaboration are needed among funding sources, academic labs and industrial partners to ensure success. The continued support of private agencies, public agencies such as the National Institutes of Health and National Eye Institute as well as state agencies such as the California Institute of Regenerative Medicine are critical for the successful implementation of stem cell based therapies.

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Focus on Retina Surgery

RETINAL DETACHMENT SURGERY: IS LESS SCLERAL BUCKLING ALWAYS RIGHT?

One surgeon dives into his own dilemma of vitrectomy with or without scleral buckling.

By Tien Wong, MD

Last fall I listened to several interviews with Paul Hahn, MD, on the changing trends in retinal detachment repair over the past decade at Duke University Eye Center. That he said more cases were being done by vitrectomy did not surprise me. What did, and what was different from my personal experience, was the frequency the Duke surgeons were performing scleral buckling in conjunction with vitrectomy. In fact, most of their vitrectomy cases involved scleral buckling.

This prompted me to look at my own cases. I reviewed my last 100 cases of repair of retinal detachment (RD) with vitrectomy (CPT code 67108) that had at least six months of follow-up. I excluded cases that involved conditions such as trauma, endophthalmitis or retained lens fragment, or cases that were primarily vitreous hemorrhage with retinal break and a small, localized retinal detachment that might also be coded with 67108, but might have a more favorable prognosis than a bullously detached retina. I also excluded cases that had previous surgeries for RD, such as pneumatic retinopexy and scleral buckling (*Figure 1, page 36*).

I found that I did scleral buckling with pars plana vitrectomy in only 10 cases; I repaired 90 percent with vitrectomy alone. Six of the 100 patients required additional surgeries to repair recurrent retinal detachment, so the one-operation success rate was 94 percent.

Interestingly, all the cases that failed were cases of vitrectomy alone. The one-operation success rate for vitrectomy alone was still a respectable 93 percent (83/90). However, it troubled me that adding the scleral buckling procedure seemed to increase the success rate.

Would my success rate have been higher if I had performed more or all vitrectomies with scleral buckling? Having to incorporate scleral buckling on all my vitrectomy cases was not that appealing to this presbyope.

To Buckle or Not to Buckle

Mark Twain said, "There are three kinds of lies: lies, damned lies and statistics." So I decided to manipulate my data to improve my vitrectomy-only results. Since I had six failures, I decided to look at my last 100 cases of CPT code 67108 that were vitrectomy only and see if I could raise my success rate to 94 percent by reviewing more cases. I had to review a few more months of surgery.

Unfortunately, I found I had one additional failure with vitrectomy

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alone, so 93/100, or 93 percent, were repaired with one operation, just as with the 90 cases. However, during that same additional time interval, I did three more vitrectomies with scleral buckling, and two required additional retinal surgeries, resulting in a one-operation success rate of 11/13, or 85 percent.

This was what I'd expected. I usually choose to add scleral buckling on cases that I think may fail from proliferative vitreoretinopathy (PVR) based on three factors:

- how chronic the detachment is;
- the amount of vitreous debris; and
- how rigid the retina is.

Thus, these cases should have had a higher failure rate. These findings were more consistent with my clinical experience that scleral buckling is unnecessary for most primary retinal detachments.

I don't do all retinal detachment repairs by pars plana vitrectomy. During the time period that I did those 113 operations of retinal detachment repair with vitrectomy, I also performed scleral buckling alone (CPT code 67107) in 43 cases. All but one of those cases required only a single surgery, a 98 percent one-operation success rate.

Overall, my one-operation success for these reviewed cases was 94 percent. Almost two-thirds of the time—64 percent—I performed vitrectomy alone; 28 percent were scleral buckle alone; and 8 percent vitrectomy with scleral buckling.

Based on my small numbers, I do not believe that scleral buckling is superior to vitrectomy, or that scleral buckling with vitrectomy is inferior to vitrectomy alone. Rather, if I choose the appropriate surgery to repair a retinal detachment, the single operation success rate is very high—more than 90 percent. So, how do I decide on the appropriate surgery?

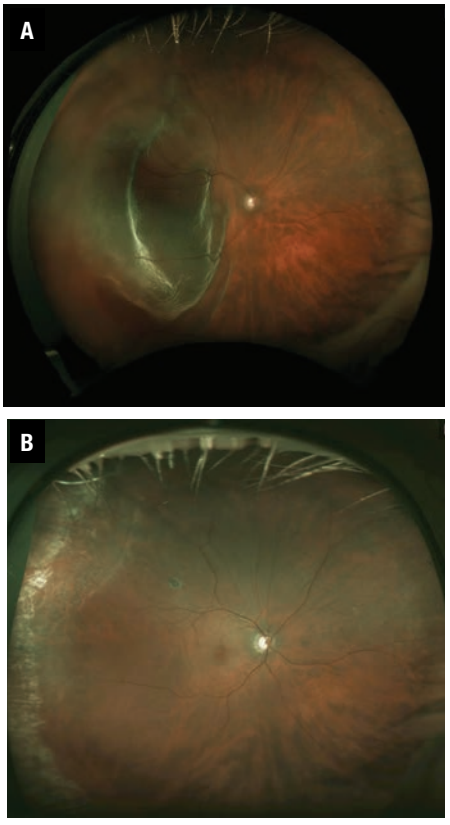

Figure 1. A typical case that would be included in the CPT code 67108 series, retinal detachment (RD) repair with vitrectomy (A). Postoperative photography (B) shows outcome of macula-off RD, resulting in complete recovery of central vision and subjectively better vision post-RD repair because of vitrectomy and floater removal.

When To Do Scleral Buckling

As a general rule, if the retinal detachment is not due to posterior vitreous detachment, I will perform scleral buckling. These cases are often due to high myopia, abnormal retinas with holes or lattice, and have abnormally strong vitreoretinal adhesions. In my opinion, altering the eye wall to match the abnormal retina is the best approach to treating these cases.

Some of the most spectacular retinal detachment failures that I have seen are cases where vitrectomy alone was performed for a young myope and the patient ends up with PVR and multiple surgeries with a horrible visual outcome. The retina doesn't conform to the shape of the eyeball, which is why it detached in the first place, and removing the vitreous (assuming that the vitreous is removed with successful separation of the posterior hyaloid, which is not always the case) and lasering retinal holes may not be adequate to permanently reattach the retina. Sometimes it takes three or four operations and a large relaxing retinectomy to successfully reattach the retina, but by this point the patient has usually lost vision.

For retinal detachments that are due to vitreous detachment with concomitant tearing of the retina, the obvious choice is vitrectomy, especially if vitreous hemorrhage, significant vitreous pigment and haze,

Take-home Point

Surgery to repair retinal detachments has improved dramatically over the past three decades. With improvements in the instrumentation for vitrectomy surgery, such as wide-angle viewing, illuminated lasers and small-gauge/high-speed vitrectomy cutters, and the more frequent use of vitrectomy for retinal detachment repair, we can confidently tell patients that we have a better than 90-percent chance of repairing their detachment with one operation and restoring their vision. These advances in retinal detachment surgery, in the author's opinion, are almost as great as the improvements we have seen in the treatment of macular diseases with anti-VEGF medications.

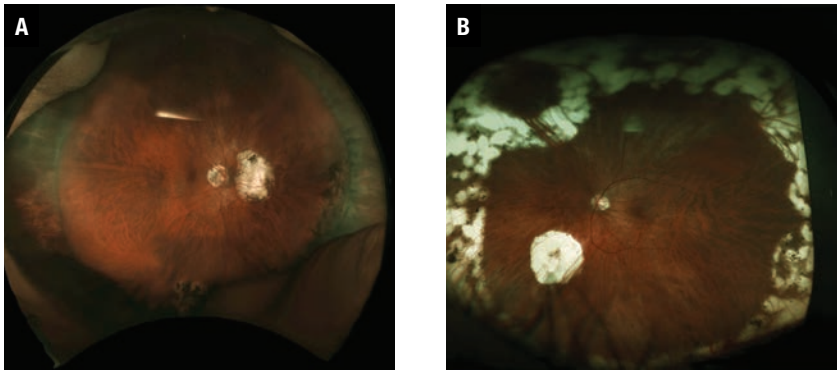

Figure 2. A poorly performed drainage retinotomy (A) is too posterior and too large. Despite single-operation success, the patient is unhappy because of a visual scotoma. This retinotomy (B) is not as symptomatic, and although the scotoma is apparent to the patient, it is not as bothersome as that in Figure 2A because it is farther from optic nerve and is in the superior field of view, which is often less noticeable. However, it is still unnecessarily large.

or symptomatic floaters are present. Except when pneumatic retinopexy is appropriate, vitrectomy is the correct procedure, and that is what I do in almost all pseudophakic patients.

In instances of retinal detachment due to PVD where the vitreous and lens are clear, or in situations such as when the patient has a need to travel, I will sometimes perform scleral buckling surgery. Of the 43 cases of scleral buckling alone (CPT code 67107) that I did during the review period, all were phakic; half (23/43) had PVD causing the retinal detachment.

Besides the cases in which I perform vitrectomy with scleral buckling that I mentioned earlier, I'm also more likely to perform scleral buckling with vitrectomy in younger patients and those who are phakic because my vitrectomy may not be as complete. The location of retinal break(s) does not factor into my decision to incorporate scleral buckling.

My Approach To Scleral Buckling

As someone who trained in the late 1980s and early 1990s, I used radial and segmental buckling when I first started out in practice. I have not used a radial element in nearly 20 years. A gas bubble or vitrectomy will prevent "fish-mouthing" of a retinal tear. I rarely do segmental buckles, except for the occasional traumatic dialysis. Everyone who needs scleral buckling is encircled. I use a 3.5-mm band for most of my cases. Occasionally, I will use a 5-mm sponge when I need a broader area of support because of the different location of breaks relative to the vitreous base. I can achieve a higher buckle with the sponge with less induced myopia than with a silicone band.

I perform external drainage on almost all cases of retinal detachment repair without vitrectomy (41/43). I use a short, 25-gauge needle for drainage, for which I sometimes use indirect ophthalmoscopic visualization (*Figure 2*). Rarely I will perform a posterior sclerotomy and suture the sclerotomy, usually on chronic detachments when the subretinal fluid is very thick.

My Approach to Vitrectomy

I perform almost all vitrectomies for retinal detachment with a posterior retinotomy and internal drainage of subretinal fluid. When I drain through a peripheral break, my removal of subretinal fluid is less complete. This has sometimes resulted in subretinal fluid being pushed into the macula, when the macula was not involved, and, less frequently, a

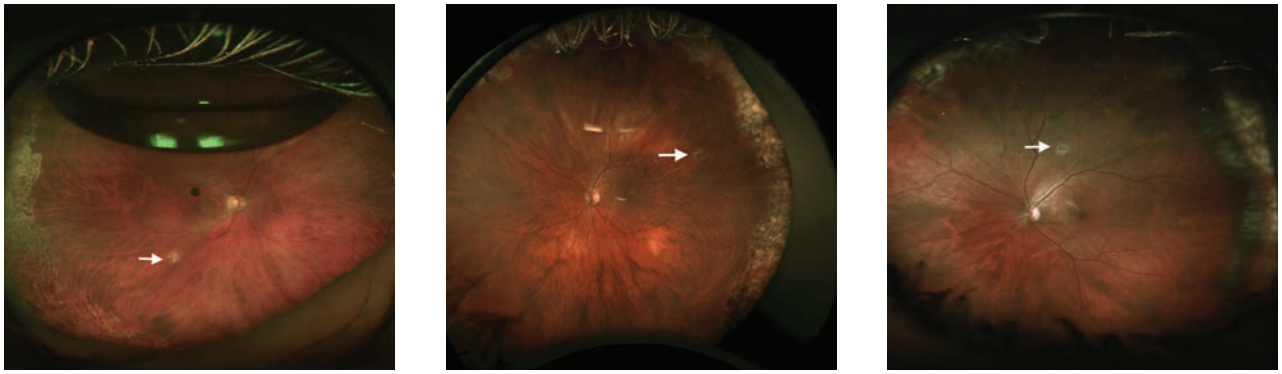

Figure 3. Retinotomies should be like these three, as highlighted with arrows: small and visually insignificant.

macular fold. I use C3F8 on almost all cases, phakic or pseudophakic.

I am not concerned about causing cataract; I use a longer-acting gas, because cataract surgery is very successful and safe today and because retinal detachment is blinding if my surgery fails.

I occasionally use SF6 or silicone oil if the patient asks for it because of travel needs. I rarely use perfluorocarbon liquid unless a giant retinal tear is involved or if the patient is young with an abnormally adherent vitreoretinal interface and I need it to stabilize the retina to adequately remove the vitreous safely.

My usual sequence for reattaching the retina involves flattening the retina by removing the fluid from the vitreous cavity and then draining through the posterior retinotomy. I then perform laser to the peripheral retina. After completion of the peripheral laser, I drain the fluid that has migrated posteriorly from the vitreous base at the optic nerve.

Lastly, I drain again from the posterior retinotomy and then apply the laser to it. I find that if I perform laser to the posterior retinotomy immediately after the initial internal drainage, the fluid that migrates posteriorly while I am doing the peripheral laser lifts up the edges of the retinotomy and I can no longer see my laser burn. This results in my treating the retinotomy again and creating a larger laser scar than desired.

I try to make my posterior retinotomies not too posterior—usually several disc diameters from the optic nerve and arcades—to reduce the risk of visual scotomas; and I try to keep the size under 1 disc diameter (*Figure 3, page 37*).

I have heard speakers advocate not applying laser to the retinotomy, and instead making a more posterior retinotomy near the nerve and around the arcade, presumably to make subretinal fluid drainage more complete. I have never personally done that.

For laser retinopexy, I do not use continuous laser because I have very slow reflexes; by the time I see that the retina has turned white, I have probably "overcooked" it. I have seen a trend of patients having one row of heavy continuous laser in the peripheral retina around or just anterior to the equator. Typically I see them as a second opinion when they develop breaks on either side of the laser. I am not sure when this type of laser treatment became fashionable since I trained a long time ago. Truthfully, I would have never thought to perform laser in this fashion as I fail to see the rationale behind it.

In the areas in which I perform laser, I treat the retina the same way I was taught to treat retinal breaks in the clinic—to the ora serrata.

I use a curved illuminated laser and perform scleral depression myself to get treatment all the way to the ora serrata without damaging the lens in phakic eyes. I try to obtain a light gray burn to create a chorioretinal scar but without coagulation or shrinkage of the retina. I use a more intense white burn when I have performed a relaxing retinectomy and I'm not concerned about the retina contracting from the laser because there is a free edge.

Lastly, I suture my sclerotomies in cases when I want a more complete gas fill, such as inferior detachments and cases with early PVR and all cases involving silicone oil or scleral buckling.

Stem Cell Therapy For Non-nAMD: References

(Continued from page 34)

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RETINA STANDOUTS FROM ARVO 2017: SURGICAL ROBOT, FAc FOR DR AND MORE

Latanoprost for myopia, OCT-A to detect CNV and stem cells for GA also worth noting.

By Ashkan M. Abbey, M.D.

ARVO 2017 in Baltimore brought together the best researchers in retina to exhibit the latest in diagnostics treatment, and management strategies for retinal disease. These five posters and presentations from the Association of Research in Vision and Ophthalmology annual meeting caught our attention: the first use of robotic retinal surgery on a human eye; the effect of the fluocinolone acetonide (FAc) implant on diabetic retinopathy; topical latanoprost to slow myopia progression; detection of quiescent choroidal neovascularization (CNV) using optical coherence tomography angiography (OCT-A); and progress in stem cell therapy for geographic atrophy (GA).

This year, we present full citations in the references, including abstract numbers that you can use to locate the original report at arvo.org. We also note disclosures.

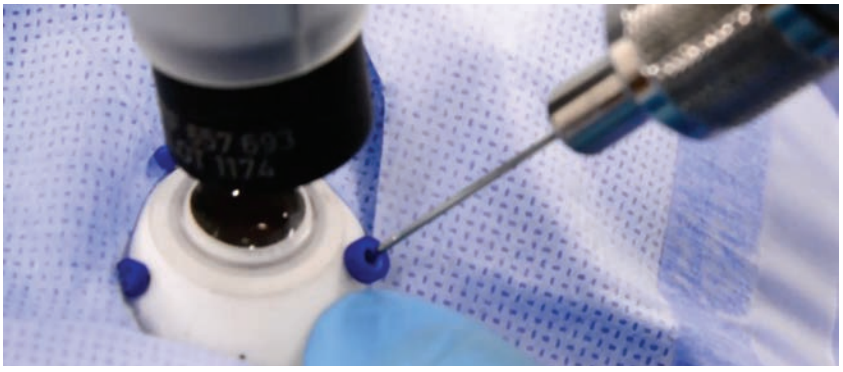

Figure. Insertion of the microneedle through a port in simulated robotic ocular surgery.

Is Robot Superior For ERM or ILM Peeling?

For years, many surgical disciplines outside of ophthalmology have used robotic surgery to add precision to their operations. This study from the University of Oxford provided the first glimpse of the use of a robot for retinal surgery (*Figure*).[1]

The investigators randomized 12 eyes requiring epiretinal membrane or internal limiting membrane peeling into two groups of six. One group received standard manual membrane peeling with a single surgeon, while the other underwent the procedure with an assistive teleoperative robotic system. In the robotic cases, the surgeon utilized a motion controller at the edge of the surgical field to initiate the flap for the membrane peel.

The primary comparative task was initiation of the flap for membrane peeling. In the robotic group, there were a total of two retinal

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Disclosures: Dr. Abbey is a consultant for Allergan.

hemorrhages and one incident of retinal touch with flap initiation, compared to five hemorrhages and two retinal touches in the manual group. The mean time to initiate the flap was on average 43 seconds longer using the robot (213 ± 51 seconds vs. 130 ± 118 seconds).

This study demonstrated the first safe utilization of a robot for retinal surgery in human eyes. The robot eliminates instability from a surgeon's microtremor and facilitates extremely precise surgical maneuvers. Given these advantages, robotic surgery may prove to be the superior option for future treatments requiring transretinal surgery with stem cells and gene therapy.

Four investigators disclosed relationships with Preceyes BV, the Eindhoven, Netherlands-based company commercializing the robotic surgery technology that has been developed at the Eindhoven University of Technology.

FA Implant for Treatment Of Diabetic Retinopathy

The fluocinolone acetonide (FAc) intravitreal implant (Iluvien, Alimera Sciences) delivers continuous local therapy for 36 months. The Food and Drug Administration approved Iluvien as a treatment for diabetic macular edema after safety and efficacy were established using the three-year randomized clinical trial known as the FAME study.

A post-hoc analysis of the FAME study demonstrated that intravitreal injection of the FAc implant reduces the progression of diabetic retinopathy compared to sham treatment.[2]

Patients from the FAME trial who received 0.2 µg/day Iluvien were followed over 36 months and assessed for change in progression of proliferative diabetic retinopathy (PDR), mean Diabetic Retinopathy Severity Scale (DRSS) score and time to at least a two-step improvement or worsening in diabetic retinopathy (DR) grade compared with sham control-treated patients.

At 36 months, the proportion of patients with PDR progression was significantly reduced in Iluvien-treated patients when compared with those patients treated with sham (18 percent vs. 31 percent, respectively; $p<0.001$). In patients with baseline nonproliferative DR (NPDR) levels 47 to 53 (moderate-to-severe NPDR), PDR progression was 18 percent in the treatment group and 35 percent in controls ($p<0.002$).

The investigators reported a statistically significant difference in change in overall mean DRSS score between Iluvien- and sham-treated patients at almost every time point during the 36-month trial. The Iluvien-treated group also had a significantly greater proportion of patients that achieved at least a two-step improvement in DRSS score and a reduced proportion of patients with a two-step or greater worsening in DRSS score over time (*Table 1*).

Table 1. Diabetic Retinopathy Severity Scale Change at 36 Months in Patients with Baseline Diabetic Retinopathy Grade 47 to 53

	Sham (n=71)	Fluocinolone Acetonide Implant (n=149)	*p* Value
≥ Two-step Improvement in DRSS	21.9%	45.4%	0.008
≥ Two-step Worsening in DRSS	39.3%	14.8%	0.001

This study demonstrated that the Iluvien implant slows the progression to PDR at a similar rate to monthly anti-VEGF dosing. Furthermore, the implant improves diabetic retinopathy severity, although to a lesser degree when compared to monthly anti-VEGF dosing.

The overall benefits for diabetic retinopathy may support earlier use of Iluvien for younger pseudophakic diabetic patients to prevent progression of their retinopathy over time.

The study author disclosed a relationship with Alimera Sciences.

Topical Latanoprost To Slow Myopia Progression

Topical latanoprost, commonly used to treat glaucoma, was found to also reduce the progression of myopia in guinea pig eyes. Eight animals underwent myopia induction using monocular form deprivation. Four animals received daily topical

Take-home Point

Five presentations from the Association of Research in Vision and Ophthalmology 2017 are worth a second look: early use of surgical robotics for epiretinal and internal limiting membrane peeling; a post-hoc analysis of the FAME trial of how fluocinolone acetonide implant impacts progression of diabetic retinopathy; the effect topical latanoprost has on myopia progression; how optical coherence tomography angiography can help detect quiescent neovascularization in nonexudative age-related macular degeneration; and the effect subretinal transplantation of human central nervous system stem cells can have on geographic atrophy.

latanoprost in their deprived eyes, while remaining control animals received topical artificial tears.[3] The treatment lasted for 12 weeks.

Interocular optical axial length differences changed minimally in the latanoprost group, from -0.05±0.06 to -0.01±0.05 mm, compared to -0.01±0.04 to 0.22± 0.13 mm in the control group. Thus, the latanoprost group developed minimal myopia; interocular refractive error differences changed from -0.44±1.1 to 0.5±1.06 D compared to 0.81± 1.46 to -8.5± 0.70 D in the control group.

Current projections estimate that myopia will affect half of the world's population by 2050, with expected rises in the rates of retinal detachments, myopic degeneration and other sight-threatening complications raising real concern. This study suggests that topical latanoprost may be an easily administered and effective topical therapy to halt the progression of myopia. Larger, controlled studies in humans will be important to validate this intriguing finding.

The authors had no pertinent disclosures.

OCT-A Detects Quiescent Neovascularization in AMD

Quiescent choroidal neovascularization (CNV) can be detected using OCT-A in nonexudative AMD.[4] A multicenter, prospective consecutive case series analyzed swept-source OCT angiography (SS-OCT-A) of eyes with intermediate AMD (iAMD) or geographic atrophy (GA) secondary to nonexudative AMD in one eye and a history of exudative AMD in the fellow eye to determine the prevalence of quiescent CNV. The study also determined time to exudation and cumulative incidence of exudation in these quiescent neovascular membranes.

The researchers performed SS-OCT-A on 152 eyes (111 with iAMD and 41 with GA). Quiescent CNV was detected in 20 of the iAMD eyes (18 percent) and seven of the eyes with GA (17 percent). Eleven of 152 eyes developed exudation; 10 of those 11 eyes were previously diagnosed with quiescent CNV. The one eye developing exudation that was not diagnosed with a pre-existing neovascular lesion did not have adequate follow-up visits.

After 12 months, the cumulative incidence of exudation in all 152 eyes was 8.7 percent, and by 24 months it was 27.3 percent. In eyes with quiescent CNV, 29.7 percent of eyes developed exudation by 12 months. There was no difference in the predicted cumulative onset of exudation from pre-existing CNV in eyes with either iAMD or GA (p=0.89, log-rank test).

This study demonstrates that nearly all eyes with iAMD or GA that develop exudation over two years have a detectable quiescent CNV on SS-OCT-A prior to the event. These eyes may benefit from regular screening with SS-OCT-A for early detection of quiescent CNV. Further study is required to determine the possible benefits of treating quiescent CNV with anti-VEGF agents prior to exudation.

Several authors disclosed a relationship with Carl Zeiss Meditec.

Table 2. Differences in Geographic Atrophy Progression at 12 Months Between Study Eye and Fellow Eye: Sectoral Quadrant-Wise Growth Rates

	Study Eyes (mm^2)	Fellow Eyes (mm^2)	*p* Value
Superior Nasal Quadrant (12, 1, 2 o'clock hour)	0.11 ± 0.07	0.14 ± 0.13	0.48
Inferior Nasal Quadrant (3, 4 ,5 o'clock hour)	0.08 ± 0.11	0.16 ± 0.13	0.08
Inferior Temporal Quadrant (6, 7, 8 o'clock hour)	0.11 ± 0.09	0.09 ± 0.09	0.61
Superior Temporal Quadrant (9, 10, 11 o'clock hour)	0.06 ± 0.11	0.21 ± 0.13	0.03

Subretinal Transplantation Of Stem Cells for GA

Subretinal transplantation of human central nervous system stem cells (HuCNS-SC) appears to be associated with a slower expansion of GA in the quadrant in which the treatment was delivered.[5] A multicenter prospective clinical trial examined 22 eyes in 11 subjects with bilateral GA from AMD (*Table 2*). The transplanted eye was considered to be the study eye, while the fellow untreated eye was treated as a control.

The investigators infused a total of 1 x 10^6 HuCNS-SC in a volume of 0.02 mL directly into the subretinal space superotemporal to the fovea near the junctional zone outside the area of GA. They measured total GA area using fundus autofluorescence images at baseline and month 12. They calculated sectoral/directional GA progression rates with respect to the foveal center in both eyes using special software—a polar

(Continued on page 43)

By Kirk A. Mack, COMT, COE, CPC, CPMA »

Avoiding Post-Surgical Modifier Confusion

How to use three modifiers for surgery that falls within the global period of another procedure.

We often see confusion on our clients' faces when we talk to them about the appropriate use of post-surgical modifiers. In this article, I discuss the modifiers necessary when billing additional surgical procedures during the global period of another procedure. Three modifiers in particular affect a surgical retina practice's proper coding and reimbursement within the global period of another surgical procedure. The Current Procedural Terminology (CPT) manual describes the three modifiers I'm going to review:

- –58: Staged or related procedure or service by the same physician or other qualified health care professional during the postoperative period.
- –78: Unplanned return to the operating/procedure room by the same physician or other qualified health care professional following initial procedure for a related procedure during the postoperative period.
- –79: Unrelated procedure or service by the same physician or other qualified health care professional during the postoperative period.

Modifier –58

Misunderstanding is common when deciding how and when to use –58. Three scenarios in the Medicare Claims Processing Manual (MCPM) apply to this modifier:

> *Modifier "-58" was established to facilitate billing of staged or related surgical procedures done during the postoperative period of the first procedure. The physician may need to indicate that the performance of a procedure or service during the postoperative period was:*
>
> ***a.** Planned prospectively or at the time of the original procedure;*
>
> ***b.** More extensive than the original procedure; or*
>
> ***c.** For therapy following a diagnostic surgical procedure.*
>
> *These circumstances may be reported by adding modifier "–58" to the staged procedure. A new postoperative period begins when the next procedure in the series is billed.*[1]

Items *a* and *b* represent the most common usage for –58. Item *a* illustrates a "staged" scenario—a procedure that follows another procedure and is pre-planned when the decision for the primary procedure was made. In other words, the surgeon anticipates needing the second procedure before performing the first. "More extensive" in item *b* does not require pre-planning. From the payer's perspective, "More extensive" represents increased value or a greater reimbursement. The second procedure during the global period is "more extensive" when it has a greater reimbursement.

An example of a staged procedure is a vitrectomy internal limiting membrane peel for diabetic macular edema (DME) (CPT 67042) followed by a sequence of pre-planned intravitreal injections (CPT 67028) of anti-VEGF to treat the DME in the same eye. It is obvious that this does not represent "more extensive" case in terms of value, but the injections are clearly pre-planned. If the injections were not pre-planned, the payer would likely view the subsequent injections as postoperative care, reimbursing only the drug.

"More extensive" is easier to understand, but is often misinterpreted. A classic scenario is a retinal detachment (RD) repair (CPT 67108) followed by a complex RD repair involving proliferative vitreoretinopathy (PVR) and membrane peeling (CPT 67113) in the same eye. In this case, the second RD repair was not pre-planned but it was "more extensive" and coded with –58. We often see practices erroneously code this scenario with –78. A second example would be laser treatment of a retinal tear (CPT 67145). Within the 90-day global period, the tear progresses to an RD, requiring vitrectomy RD repair (CPT 67108). In this case, "more extensive" also applies.

Modifier –58 reimburses the surgeon based on 100 percent of the allowed amount and restarts the global period (as long as it exceeds the first global period). In the first scenario—injection following the vitrectomy—the global period would continue running from the vitrectomy, but in the second scenario a new 90-day clock commences.

Modifier –78

Billers sometimes use this modifier erroneously when –58 is the correct choice. The MCPM describes –78 as:

> *When this subsequent proce-*

dure is related to the first procedure and requires the use of the operating room, this circumstance may be reported by adding the modifier "–78" to the related procedure.[2]

Medicare and other third-party payers do not typically pay for treatment of complications during a global period. However, when treating the complication requires a return to the operating room, they cover the related care. For example, a patient who underwent a vitrectomy RD repair (CPT 67108) unexpectedly develops endophthalmitis within the first week. The surgeon returns to the operating room to perform a vitrectomy (CPT 67036). The second vitrectomy is treating a related and/or complication of the first procedure by returning to the OR. The second vitrectomy is not "more extensive" or "staged" therefore –78 applies.

Modifier –78 reimburses the surgeon approximately 80 percent of the allowed amount, depending on the payer, but it does not restart the global period. The global period continues to run from the first procedure.

Modifier –79

Considering the three modifiers discussed, –79 is the easiest to use and simplest to understand. The MCPM describes –79 as follows:

Modifier "–79": Reports an unrelated procedure by the same physician during a postoperative period. The physician may need to indicate that the performance of a procedure or service during a postoperative period was unrelated to the original procedure.[3]

The classic illustration is a procedure on the fellow eye during the global period of a procedure on the primary eye. For example, a patient with diabetic retinopathy and DME needs focal laser in both eyes. The right eye is treated with CPT 67210; followed 10 days later by focal laser to the left eye (CPT 67210). Modifier –79 appended to the second treatment facilitates payment of an unrelated service.

Modifier –79 reimburses the surgeon based on 100 percent of the allowed amount and restarts the global period (as long as it exceeds the first global period). In this scenario, a new 90-day global period begins following the second laser.

Conclusion

These three surgical modifiers are important to a retina practice that does any amount of surgery. Differentiating between –58 and –78 can be challenging, but know that if –58 applies, use it. Watch the global periods closely as modifier –78 does not restart the global period, but –58 and –79 do.

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Retina Standouts From ARVO 2017

(Continued from page 41)

transformation method.

Twelve months after treatment, the researchers found no statistically significant difference in the mean change in total GA area between study and fellow eyes. However, the sectoral growth rate of GA in the superotemporal quadrant where the injections were placed was significantly slower in study eyes (0.06 ± 0.11 vs. 0.21 ± 0.13 mm^2, p=0.03). The progression rate in the superotemporal quadrant was also significantly slower than the other three quadrants of the study eye combined (p=0.003).

The study authors concluded HuCNS-SC transplantation appears to be associated with slower growth of GA in the quadrant in which it is injected. Although further study is required, this is an exciting new development for the possible future treatment of GA, a disease for which we currently have no effective treatment.

One author disclosed relationships with Allergan, Genentech, Iconic, Thrombogenics, Novartis, Carl Zeiss Meditec and Optos.

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Restoring Cell Function to Block VEGF

Integrin peptide therapy Luminate shows potential of extending DME treatment.

By Richard Mark Kirkner

Anti-VEGF drugs have proven to be effective treatments for diabetic macular edema, but about half of this population does not respond to anti-VEGF therapy and monthly injections can be burdensome. A readout from the DEL MAR Phase IIB Stage 2 clinical trial of the integrin peptide agent Luminate (Allegro Ophthalmics) as sequential therapy with anti-VEGF shows the potential of extending out those injections.

Luminate showed noninferiority to bevacizumab (Avastin, Roche/Genentech) in average change in best-corrected visual acuity at 20 weeks when Luminate was used in sequential therapy with a single bevacizumab pretreatment.

Luminate results were achieved after one initial treatment of 1.25 mg bevacizumab followed by three 1-mg Luminate injections (at one, four and eight weeks) and 12 weeks off treatment vs. five bevacizumab injections given every four weeks. The data showed the mean gain in BCVA was 7.1 letters for the sequential therapy group vs. 6.7 letters for the bevacizumab control group.

The trial also found no drug toxicity or intraocular inflammation associated with Luminate, safety results consistent with previous Luminate trials. The study was conducted at 14 U.S. sites.

Luminate is a first-in-class agent that targets integrin receptors involved in cell signaling and regulation and in the construction of new and aberrant blood vessels. It not only blocks production of growth factors, but also directly interferes with vessel construction and has specific anti-inflammatory properties.

Here, investigator Derek Kunimoto, MD, of Retinal Consultants of Arizona in Phoenix provides insights into the Phase IIB Stage 2 trial, followed by a comment from Vicken Karageozian, MD, president and chief medical officer of Allegro Ophthalmics, on plans for Luminate going forward.

The mechanism of action in Dr. Kunimoto's own words:

The mechanism of action is that Luminate, which binds to several specific integrin receptors, resets the cell cycle into homeostasis and normal function so that the cells are not producing vascular endothelial growth factor (VEGF) and other inflammatory mediators in their hypoxic state.

Work by Julie Kornfield, PhD, at the California Institute of Technology, and by Peter Compochiaro, MD, at Johns Hopkins University, supports the hypothesis that Luminate-treated cells did not express anti-inflammatory mediators.

Q What is the advantage of sequential therapy of bevacizumab followed by Luminate?

A At month five, 88 percent of the sequential-treatment group had vision improvement, and at every single time point Luminate showed equivalency to bevacizumab in vision improvement through the entire five-month study. When the cells return to their normal homeostatic state, the anti-VEGF clears the VEGF burden while Luminate blocks inflammation and further production of VEGF.

Q What are the take-home points of the trial?

A First, the trial met its primary endpoint of noninferiority to bevacizumab in improvement of BCVA when Luminate was used in sequential therapy. Secondly, the 1-mg dose of Luminate in sequential therapy demonstrated improvement in BCVA at all time points when compared to bevacizumab monotherapy. Third, Luminate showed 12 weeks of durability. And lastly, 60 percent of the patients in the DEL MAR Stage 2 population were chronically treated with anti-VEGF and even they saw substantial improvement in BCVA.

Q What's next?

A Allegro is conducting a subgroup analysis of the DEL MAR data and is planning the design of Phase III trials in anticipation of a meeting with the Food and Drug Administration in January 2018, Dr. Karageozian says.

"Concurrently, we're scaling up manufacturing and personnel in preparation for Phase III, and will continue to meet with potential strategic partners and explore other fundraising options to raise the capital needed for Phase III trials," he says. Expect to see the Phase III trials roll out in the first half of next year. RS

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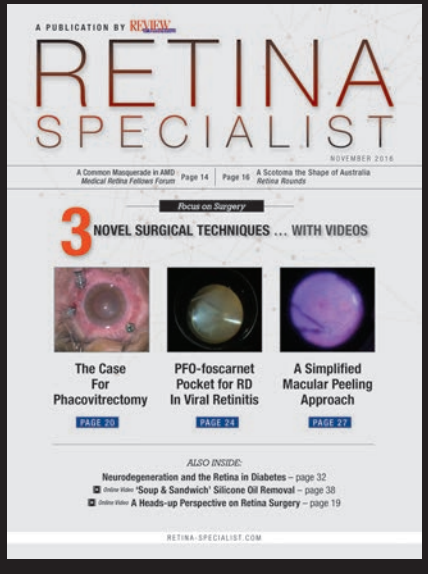

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EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing 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) in Patients with DME

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.7) and 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 [*see Dosage and Administration (2.7)*].

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. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

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

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

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

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

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

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

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

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

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

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

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], 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 [*see Nonclinical Toxicology (13.1)*].

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.

Manufactured by:
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Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

- EYLEA® (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. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

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

Please see brief summary of full Prescribing Information on the following page.

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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