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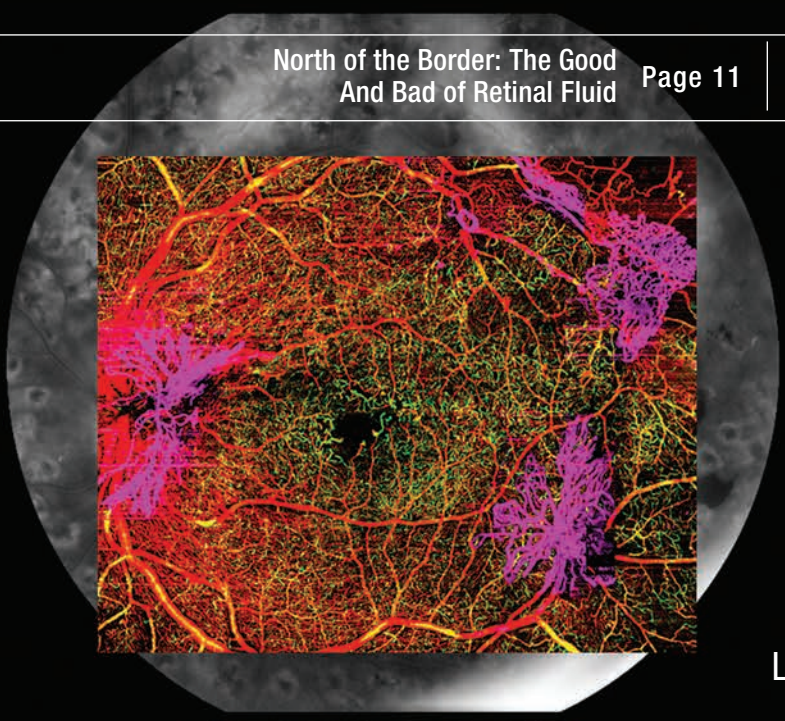
RETINA SPECIALIST

MARCH 2018



HOW OCT ANGIOGRAPHY IS IMPROVING OUR VIEW OF DIABETIC RETINOPATHY

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Clinical Conversation:
Lessons from Protocol U for DME Management

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Uveitis Update: The Paradigm Shifts Again

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Preview of 2018 Drug Development Milestones in AMD, DME

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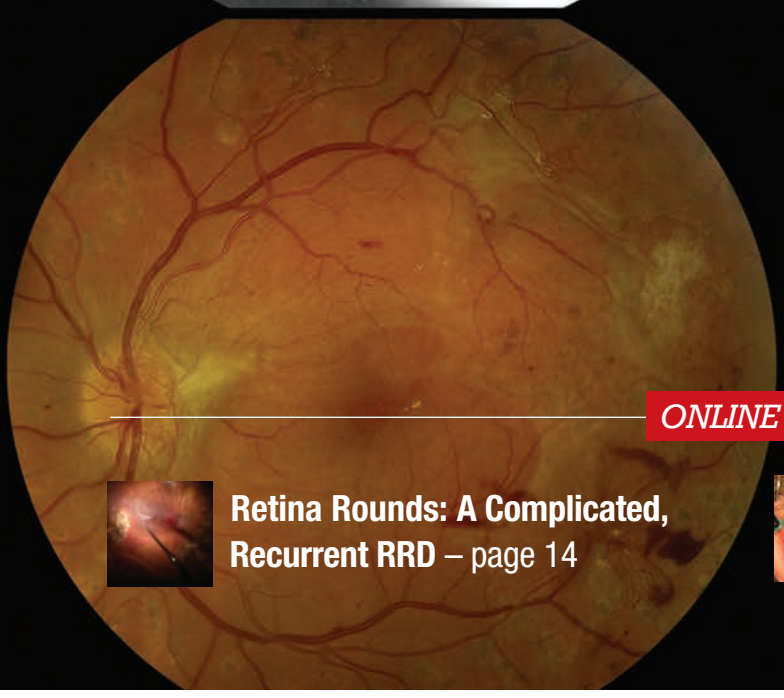

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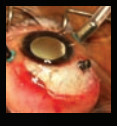

Surgical Pearl Video: Endoillumination Without an Assistant – page 34

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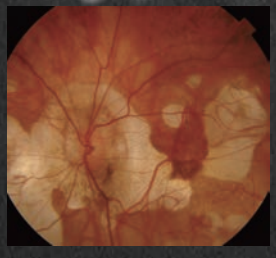

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Jobson Medical Information LLC

By Charles C. Wykoff, MD, PhD

Advancing DR and DME Management

Medical retina revolves primarily around imaging and pharmaceuticals. Fortunately, both spaces continue to evolve.

The Diabetic Retinopathy Severity Scale is a powerful tool for predicting worsening of diabetic retinopathy and correlating with visual function even in the absence of diabetic macular edema and proliferative disease.

However, quantitative data from optical coherence tomography angiography is proving to be a far better prognostic tool. On page 20, Steven S. Saraf, MD, and Kasra A. Rezaei, MD, discuss the value of OCTA in DR and make a strong case that it will fundamentally change how we classify and manage the disease.

OCTA affords tremendous opportunities to improve prognostication and inform our management decisions. However, current-generation commercial software, in my experience, is not yet adequate for widespread clinical application. I use OCTA regularly in research, but I have yet to incorporate it into the care of most of my clinic patients. I look forward to continued progress.

Anti-VEGF monotherapies have clearly set a high bar for managing exudative retinal diseases. Consistent dosing in the presence of ongoing exudation translates into remarkable visual and anatomic benefit at a population level. Nevertheless, efficacy and durability limitations exist. On page 16, our *Clinical Conversation*, using Diabetic Retinopathy Clinical Research Network Protocol U data as the backdrop, explores the value of corticosteroids in the management of DME.

Looking ahead, on page 31 we explore the retina pharmaceutical pipeline, which appears remarkably strong despite major failures in the last year.

To me, targeting angiopoietin-2 (Ang-2) appears particularly promising. At the Angiogenesis and Macula Society meetings in February, data from three Phase II trials evaluating combined VEGF-A and Ang-2 blockade were reported. Two DME trials, RUBY[1] and BOULEVARD,[2] reported that combined VEGF-A and Ang-2 blockade led to better anatomic outcomes and more robust improvements in DR severity than anti-VEGF-A monotherapy.

Furthermore, the Phase II BOULEVARD trial met its primary endpoint showing efficacy of combined VEGF-A/Ang-2 blockade, leading to significantly more visual gain through six months. Certainly, more data is needed. I look forward to the Phase III trials.

1. Brown D. Ang2 inhibition combined with anti-VEGF suppression (aflibercept) in diabetic macular edema. Paper Presented at Angiogenesis, Exudation and Degeneration; February 10, 2018; Miami, Florida.
2. Dugel P. Anti-VEGF/anti-angiopoietin-2 bispecific antibody RG7716 in diabetic macular edema: results from the Phase 2 BOULEVARD clinical trial. Paper Presented at Angiogenesis, Exudation and Degeneration; February 10, 2018; Miami, Florida.

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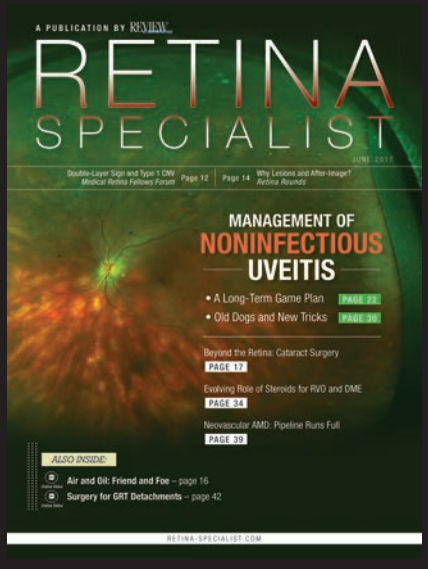
Retina Specialist focuses on the latest advances in the diagnosis, medical management and surgical treatment of diseases of the retina, along with practical, real-world advice from leading clinicians and other experts on managing the successful retina practice.



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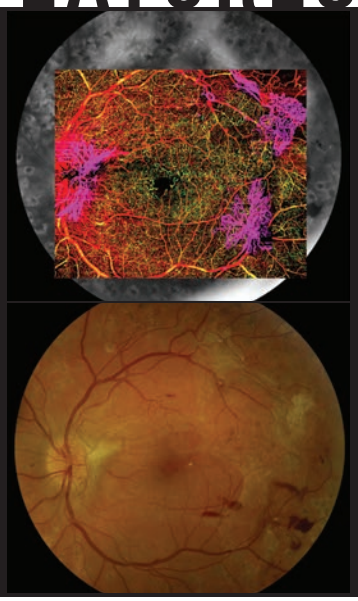
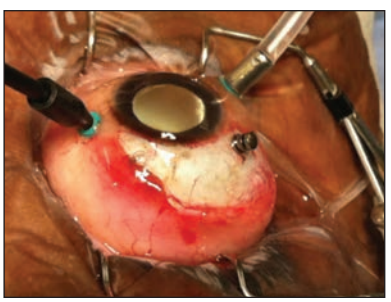
RETINA SPECIALIST

MARCH 2018

FEATURES



DEPARTMENTS



LUCENTIS 0.5 MG PREFILLED SYRINGE

EFFICACY DELIVERED

The efficacy and safety of LUCENTIS 0.5 mg studied in 7 pivotal trials,* available in a prefilled syringe.[1]

LUCENTIS®
RANIBIZUMAB INJECTION

INDICATIONS

LUCENTIS® (ranibizumab injection) 0.5 mg is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- 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. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)

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 next page.

*The following randomized, double-masked pivotal trials were conducted for the wet AMD, macular edema following RVO, and mCNV 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. **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. **mCNV:** *RADIANCE*—Phase III, multicenter, 1-year, active-controlled study; key clinical outcomes at month 3.[2-8]

VEGF, vascular endothelial growth factor.

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.** Data on file. Genentech, Inc. South San Francisco, CA.

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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 (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Initial US Approval: June 2006
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IN BRIEF

Topcon Medical Systems announced that its DRI Triton series swept-source optical coherence tomography platform received 510(k) Food and Drug Administration clearance. The company says DRI OCT Triton features easy image capture and a 1-µm, 1050-nm light source with a scanning speed of 100,000 A-scans/second. It also incorporates a built-in retinal camera and eye tracking during capture of selected scans. The device can visualize deeper pathology, such as the choroid and sclera, without artifacts from media opacities or hemorrhage.

Imprimis Pharmaceuticals has launched a new program to supply compounded ophthalmic medications, including retinal drugs. The program aims to provide compounded medications from an Imprimis FDA-inspected facility and ship within 24 to 48 hours. Imprimis says it intends to make this program available in all 50 states. Earlier, Imprimis announced its New Jersey outsourcing facility received its Drug Enforcement Agency certificate.

A Canadian scientist has developed a retina scanner that can capture high-resolution, three-dimensional cross-sectional scans in a footprint the size of a shoe box. Marinko Sarunic at Simon Fraser University in Burnaby, British Columbia, developed the scanner that ophthalmologists at **Vancouver General Hospital** spent months testing last year.

Disappointing Trial Results Doom Two Drug Development Programs

Disappointing clinical trial results have caused two companies to halt development of once-promising drug programs in age-related macular degeneration—squalamine topical solution for treatment of wet AMD and the intravitreal antigen-binding agent lampalizumab for geographic atrophy in AMD.

Ohr Chief Executive Officer Jason Slakter, MD, disclosed the decision to scrap the squalamine program during an announcement of the company's 2017 financial results.

In January, the company announced that top-line results of the MAKO trial failed to reach its endpoints. The multicenter, randomized, double-masked trial evaluated combination therapy of squalamine b.i.d. in combination with monthly ranibizumab (Lucentis, Roche/Genentech) injections and topical placebo b.i.d with monthly ranibizumab injections. At the time, Dr. Slakter said Ohr was "very disappointed" with the results of the MAKO trial.

Those on squalamine combination therapy (n=119) achieved a mean gain of 8.33 letters from baseline vs. 10.58 letters from baseline in the placebo-ranibizumab (n=118) group.

"Based on these results, we have discontinued development of squalamine, taken measures to preserve cash and are evaluating strategic alternatives to maximize shareholder value," Dr. Slakter says.

Ohr has engaged Roth Capital Markets to advise the company going forward.

Lampalizumab is an antigen-binding fragment (Fab) of a humanized, monoclonal antibody directed against complement factor D, a rate-limiting enzyme in the activation and amplification of the alternative complement pathway, dysfunction of which has been linked to the pathogenesis of AMD.

Disappointing results from two Phase III trials, SPECTRI and CHROMA, apparently doomed the lampalizumab program. Roche reported last September that the SPECTRI trial showed the drug did not reduce mean change in GA lesion area compared to sham treatment at 48 weeks.

At the time, Roche decided to suspend further dosing in SPECTRI study participants until it could evaluate results from CHROMA, the second Phase III trial.

At a review of Roche's 2017 results in London in February, Roche CEO Severin Schwan disclosed the company was removing lampalizumab for GA, also known as RG7417, from Phase III trials. The drug has also been removed from Roche's online product development portfolio.

The financial analytics firm Jefferies had projected lampalizumab would achieve $2 billion in yearly sales for Roche.

Could Müller Glia Cells be a New Treatment Target in AMD?

Researchers at Duke University may have identified a potential new treatment target in macular degeneration. Early stage research has shown that injection of human umbilical stem cells, or hUTC, into the retina may help preserve and restore vision in macular degeneration, although the underlying mechanisms behind the therapy remain unknown.

The findings, published online in the *Journal of Neuroscience*, show that hUTC treatment preserves the function of Müller glia cells in rats with degenerative vision loss.[1] "This provides strong evidence that Müller glia are important therapeutic targets for treating degenerative eye diseases," says lead study author Sehwon Koh, PhD.

The Duke scientists first examined the retinas of young rats that were genetically predisposed to an eye disease similar to retinitis pigmentosa in humans. They found that the neural synapses within the retina began to deteriorate even before the photoreceptors started to die.

As the number of neural synapses declined, the Müller glia also deteriorated, pulling their branches away from neurons and dividing haphazardly. When the researchers injected hUTC behind the retinas of the rats, the Müller glia remained healthy, as did the neural synapses. The treatment succeeded in preserving the majority of the rats' vision and stopped the photoreceptors from dying.

"Previous studies primarily focused on neurons and the retinal pigment epithelium cells as culprits in degeneration," says Cagla Eroglu, PhD, an associate professor of cell biology and neurobiology at Duke University Medical Center whose laboratory is conducting the research.

"Müller glia were not considered an important player in the early stages of retinal degeneration and were not thought to be an important target for hUTC treatment, but our findings suggested otherwise," Dr. Eroglu says.

To test whether the Müller glia were truly the key players in the synaptic loss, the team used gene editing to remove a specific gene from Müller glia cells. Deleting this gene is known to cause retinal degeneration, but its function in Müller glia has never been explored.

Without this gene, the Müller glia were defective and bore striking similarities to those in rats that had developed RP. In addition, the neural connections within retinas of these rats were malformed, mimicking the problems seen in early stages of retinal degeneration.

"What we are seeing here is that Müller glia are important players in retinal health," Dr. Eroglu says. "They are impaired in disease, and effective cellular therapies should target not only other retinal cell types but these cells as well."

The research was carried out in collaboration with Janssen Research & Development and supported by grants from the National Institutes of Health and other organizations.

1. Koh S, Chen WJ, Dejneka NS, et al. Subretinal human umbilical tissue-derived cell transplantation preserves retinal synaptic connectivity and attenuates Müller glial reactivity. J Neuroscience. Published online February 5, 1018. DOI: 10.1523/JNEUROSCI.1532-17.2018

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The Good and Bad of Retinal Fluid

The presence of intraretinal and subretinal fluid may answer the question: To treat or not to treat? ***By Joel Yap, MD, and Efrem D. Mandelcorn, MD, FRCSC***

Despite the overwhelming success of anti-VEGF agents, challenges remain in the treatment of patients with neovascular age-related macular degeneration, the leading cause of severe vision loss in the elderly population. One common dilemma is the issue of residual intraretinal or subretinal fluid (IRF, SRF) and the uncertainties of treatment with ongoing injections or observation, as these two cases illustrate.

Case 1: Chronic SRF

Mrs. ER was diagnosed with nAMD in her left eye in May 2011. She was 74 years old at the time and her initial fundus fluorescein angiogram revealed a type 1 choroidal neovascular membrane (*Figure 1*). Her presenting best corrected visual acuity was 20/50 in the left eye and she received four initial intravitreal ranibizumab injections (Lucentis, Roche/Genentech), which stabilized her disease.

Following this, we managed her nAMD with an as-occasion-requires (PRN) regimen for the next 30 months. After that, we made the decision to switch to a regular injection regimen because she developed severe visual impairment from end-stage nAMD in the right eye. In total, she received 19 intravitreal ranibizumab injections and 24 intravitreal aflibercept injections (Eylea, Regeneron) in the left eye.

However, the different anti-VEGF injection regimens and the change in the anti-VEGF agent did not make a difference in the appearance of persistent SRF on optical coherence tomography (*Figure 2, page 12*). Despite enduring chronic SRF for more than six years, Mrs. ER's left vision was preserved and BCVA was 20/25 in the left eye at her last follow-up visit. She now receives monthly intravitreal aflibercept injections in her left eye.

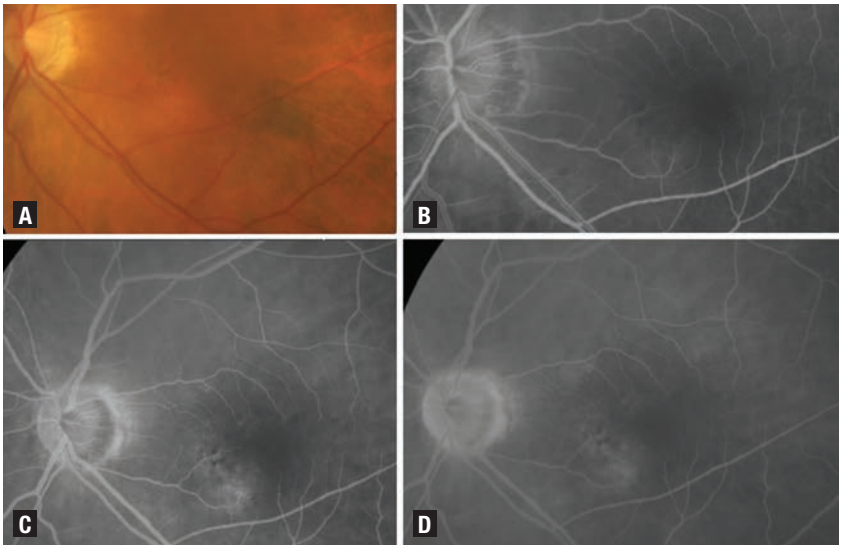


Figure 1. Color photograph (A) and fluorescein angiograms at different stages suggest an underlying type 1 choroidal neovascular membrane: B) at 16 seconds; C) at 47 seconds; and D) at five minutes.

Case 2: Persistent, Stable IRF

Mr. JB presented with a right macular hemorrhage secondary to nAMD in January 2013 (*Figure 3, page 13*). He was 82 years old at that time and BCVA was 20/200 in the right eye. Since then, we've treated him with regular intravitreal ranibizumab injections every four to six weeks, and he had a total of 44 injections in the right eye. Serial OCT scans showed persistent but stable IRF, associated with underlying subretinal fibrosis (*Figure 4, page 13*).

Despite regular anti-VEGF injections, he developed atrophic and pigmentary changes in the right macula (*Figure 3*). BCVA remains at 20/200 in the right eye. He now receives intravitreal ranibizumab injections in the right eye every six weeks.

Why SRF, IRF Drive Treatment Decisions

The landmark MARINA and ANCHOR studies, which involved monthly anti-VEGF injections, set a high standard for visual acuity results in nAMD treatment.[1,2] Subsequent studies have attempted to obtain the same favorable results while treating with a reduced number of intravitreal injections, either with a treat-and-extend or PRN regimen. In almost all of these studies, the presence of

fluid on OCT served as a marker of nAMD activity, with both SRF and IRF being associated with disease activity and thus driving decisions regarding the need for retreatment.

Given the heterogeneity of nAMD and its response to treatment, the best management approach varies between patients. A proportion of eyes may never achieve an IRF- or SRF-free macula, even with monthly anti-VEGF injections. However, we now understand that not all areas of hyporeflective signal on OCT represent fluid accumulation from exudative disease. Rather, they may represent chronic degenerative changes or potential anatomical spaces.[3] Here, we'll review studies over the past few years that have shed light on the conundrum of persistent IRF or SRF in patients with nAMD.

Eyes With SRF See Better Than Eyes With IRF

An analysis of the patients enrolled in the Comparison of Age-related Macular Degeneration Treatments Trial (CATT) found that IRF (cysts) had a much greater negative impact on visual acuity than SRF at all time points analyzed.[4] These findings were particularly prominent when the fluid affected the fovea, and were independent of the drug or treatment regimen.

The proportion of eyes with IRF decreased from 76.7 percent at baseline to 48.7 percent at the end of the one-year study across all the treatment groups. The residual cysts tended to be small. The authors hypothesized that the IRF was primarily driven by VEGF-mediated vascular permeability at the start and that non-VEGF-mediated mechanisms, such as apoptotic or necrotic cell death, accounted for the residual IRF at the end of the study.

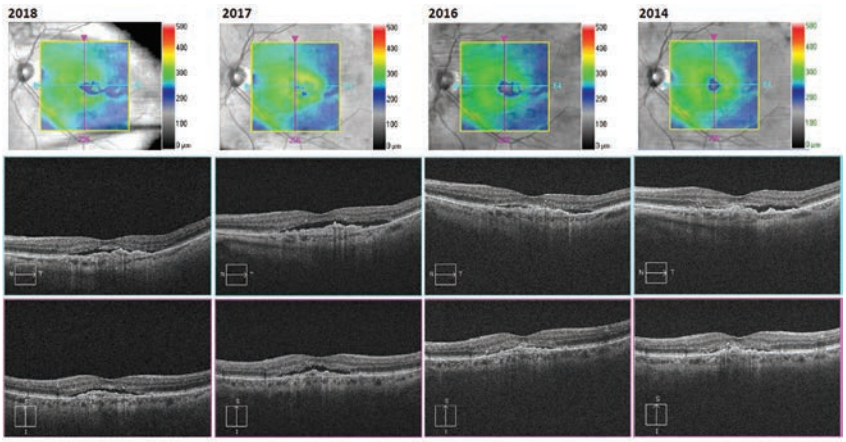


Figure 2. Serial optical coherence tomography images of Mrs. ER's left macula document chronic subretinal fluid from 2014 to 2018.

Supporting this finding in a cohort of 74 nAMD patients with refractory fluid despite monthly ranibizumab injections, researchers at the University of Lausanne in Switzerland reported that IRF was associated with poorer anatomical and functional outcome when compared to SRF.[5] Even so, their patients maintained improvement in BCVA, with increases in mean visual acuity of +9, +7.9 and +7.9 letters at months 12, 24 and 36, respectively.

They found that late fluid resolution may also occur. Patients with refractory cysts were more likely to develop fibrosis (odds ratio 3.30), atrophy (OR 3.34) and a 10-letter visual acuity loss (p=0.018).[5] Another study of 99 nAMD patients on the treat-and-extend protocol also found that the presence of IRF was associated with poorer vision.[6]

An additional study utilizing three-dimensional modeling of OCT parameters echoed the finding that IRF is a bad prognostic factor for visual function gain and treatment response in nAMD.[7] The amount of IRF at baseline correlated well with baseline visual acuity and the final visual acuity at the end of the one-year study. The study did not, however, find a robust association between SRF, visual acuity and treatment outcomes. The authors concluded that IRF at presentation should be treated aggressively until maximum resolution is achieved, as resolution of IRF resulted in better vision gain.

Why Eyes with SRF See Better

In contrast, the presence of subfoveal SRF may be associated with better visual outcomes. The previously mentioned one-year study of 99 nAMD patients on a treat-and-extend protocol showed the presence of subfoveal SRF had little impact on mean visual acuity.[6] Those nAMD patients with persistent SRF also seemed to maintain their vision in the long term.

The Lausanne group retrospectively analyzed 44 nAMD patients with treatment-refractory SRF despite monthly ranibizumab injections over an average follow-up of 32.4 months.[8] They found that the mean visual acuity increased by +10.4, +8.2 and +8.6 letters by months 12, 24 and 36, respectively. The refractory SRF was located subfoveally in two thirds of the patients, and 26.7 percent exhibited complete absorption of SRF after

22.6 months, on average.

The presence of SRF not only seems to positively influence visual function, but also the need for retreatment. The EXCITE trial, which was designed to compare the efficacy of two fixed-treatment regimens (frequent vs. infrequent) of intravitreal ranibizumab in nAMD patients, demonstrated that eyes with SRF at baseline had similarly favorable visual acuity outcomes regardless of the treatment regimen.[9]

Conversely, eyes without SRF at baseline showed poorer outcomes with infrequent treatment as opposed to frequent injections. Furthermore, improvement in retinal sensitivity during anti-VEGF treatment has been shown to be most pronounced for patients with SRF, whereas patients with IRF benefited to a lesser extent.[10]

Various investigators have described potential mechanisms for this association between SRF and better visual acuity. Researchers at Manhattan Eye, Ear and Throat Hospital demonstrated that the outer retinal layers in patients presenting with subfoveal SRF are less disrupted than in patients with IRF involving the fovea.[11] Furthermore, K. Bailey Freund, MD, and colleagues from the same group considered type 1 neovascularization, with SRF as its predominant form of fluid manifestation, as a more benign subtype of choroidal neovascular membrane in nAMD.[12]

In a group of nine nAMD patients with type 1 neovascularization and persistent SRF despite continuous anti-VEGF therapy, the presence of chronic SRF was not associated with visual loss.[13] The mean duration of persistent SRF in this group was 5.2 years and long-term visual acuities were 20/40 or better.

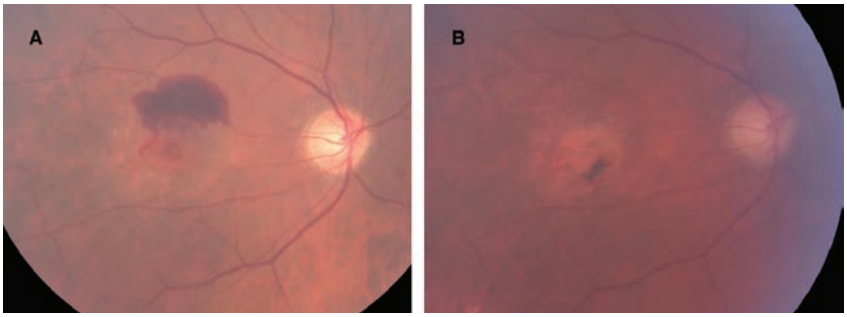


Figure 3. Color photographs of the right macula in January 2013 (A) when Mr. JB first presented and at follow-up in February 2018 (B).

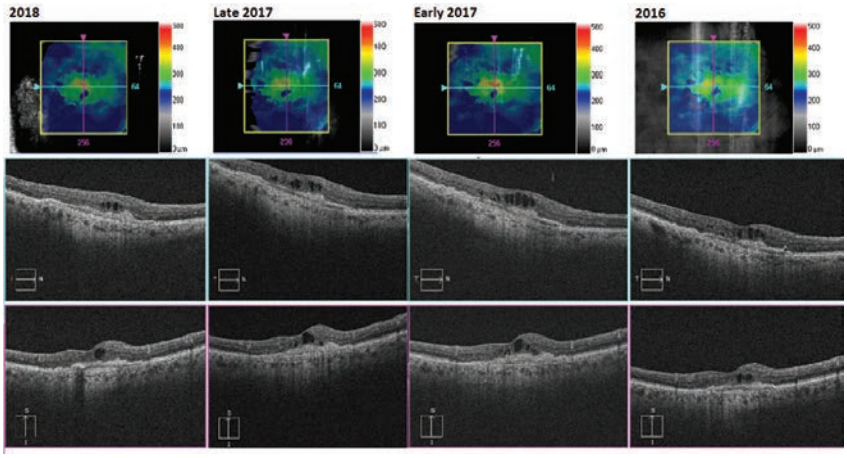


Figure 4. Serial optical coherence tomography images of the right macula document changes in chronic intraretinal fluid from 2016 to 2018.

Sophie Klimscha, MD, and colleagues analyzed the spatial overlap of IRF, SRF and pigment epithelial detachment (PED) in the OCT scans of 1,341 patients with treatment-naive nAMD using automated segmentation algorithms.[14] They found that the locations of PED and IRF are closely related, whereas the locations of SRF did not correlate well to the PED and IRF locations. They hypothesized that in the presence of subfoveal SRF, the neovascular complex, which is represented by the location of PED and IRF, is less likely to involve the fovea. This relationship could explain the beneficial effects of subfoveal SRF and the detrimental effects of fovea-involving IRF.

What Does This Mean In Managing nAMD?

Collating the existing research findings, it appears that we should treat IRF aggressively until it's stable, and that we can tolerate a degree of persistent SRF. Not all fluid observed in eyes with nAMD reflects active exudation. Persistent intraretinal cystoid changes are known to represent neurosensory degeneration rather than active neovascular leakage, which does not resolve with anti-VEGF injections.

In contrast to IRF, a small residual volume of SRF may be tolerated with minimal negative effect on vision. Residual SRF may not represent on-

(continued on page 42)

A Complicated, Recurrent RRD

How adding a scleral buckle corrected a complex proliferative vitreoretinopathy-related recurrent retinal detachment. ***By Gautam Vangipuram, MD, and Steven S. Saraf, MD***

A 56-year-old woman presented to our clinic for evaluation and second opinion of recurrent rhegmatogenous retinal detachment in her left eye. Four months earlier she went to a community retina specialist with a macula-involving RRD of the left eye that was repaired promptly with pars plana vitrectomy and gas tamponade.

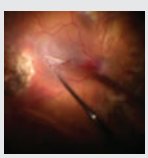
About a month later she noticed a recurrent "curtain" in her left visual field and was found to have a recurrent detachment. She underwent a repeat pars plana vitrectomy with silicone oil tamponade. In this procedure, the retina specialist contemplated adding a scleral buckle, but did not pursue it due to health concerns about this patient having general anesthesia. Over the next month, she reported persistent poor vision. Within a month of her second surgery, she developed severe proliferative vitreoretinopathy with associated recurrence of her retinal detachment.

Examination Findings

On presentation, visual acuity was found to be bare light perception in the left eye. Intraocular pressure was normal with a left afferent pupillary defect. The anterior segment exam was notable for 3+ milky nuclear sclerotic cataract with posterior synechiae and pigment on the anterior lens capsule. The vitreous cavity had a complete silicone oil fill. The optic nerve appeared normal. A subretinal perfluorooctane (PFO) bubble appeared just nasally to the nerve. The macula was detached with extensive PVR and folds. Large subretinal bands extended into the inferotemporal periphery, where the detachment had recurred. The periphery was notable for significant chorioretinal scarring with a star fold in the 5 o'clock position (*Figure 1*).

View the Video

The authors demonstrate pars plana vitrectomy with the use of scleral buckle in a complex proliferative vitreoretinopathy-related recurrent retinal detachment to relieve traction on the retina. Available at: http://bit.ly/RS_RetinaRounds_001.



Diagnosis and Management

First, we talked to the patient in detail about the risks and benefits of repeated surgeries for recurrent detachment with PVR. Given her poor visual acuity and history of recurrent detachment, we counseled her on the guarded prognosis for visual recovery in this eye. Ultimately, the patient decided to have the surgery.

The surgical plan included pars plana vitrectomy, pars plana lensectomy, membrane peeling and silicone oil exchange. Although her pathology was concentrated posteriorly in the macula, we also recommended a scleral buckle to reduce anterior-posterior tension on the retina.

In the operating room, a 240-encircling band was placed through four scleral tunnels created 3.5 mm behind the mid-point of the rectus muscle insertions. The buckle was brought to an appropriate height and secured with a 270 sleeve. Iris hooks were placed and a pars plana lensectomy was performed, followed by oil removal.

Upon inspection internally with the wide-angle, non-contact viewing system, we noted the buckle supported the inferotemporal star fold nicely. However, the retina remained elevated because of contraction of the preretinal membranes and subretinal bands within the macula. We determined the retinal detachment was due to an atrophic break near a chorioretinal scar in the inferotemporal quadrant.

We then peeled the extensive PVR membrane from over the macula and removed the subretinal bands through the pre-existing inferotemporal break. We then performed a retinectomy inferotemporally to relieve the traction from the star fold, using diathermy and the vitreous cutter. Instillation of PFO allowed the retina to flatten fully.

We applied endolaser along the edge of the retinectomy and retinotomy followed by an air-fluid exchange. The retina associated with the retinectomy appeared contracted due to PVR, but the placement of the scleral buckle reduced anterior-posterior tension and allowed for adequate support of the retina. We used 5,000-centistoke oil as a tamponade to fill the vitreous cavity to physiologic pressure.

We instructed the patient to maintain a face-down position for one week. On postoperative day one, her retina was attached without significant subretinal bands or folds (*Figure 2*).

Over the next month, her retina remained attached under oil and

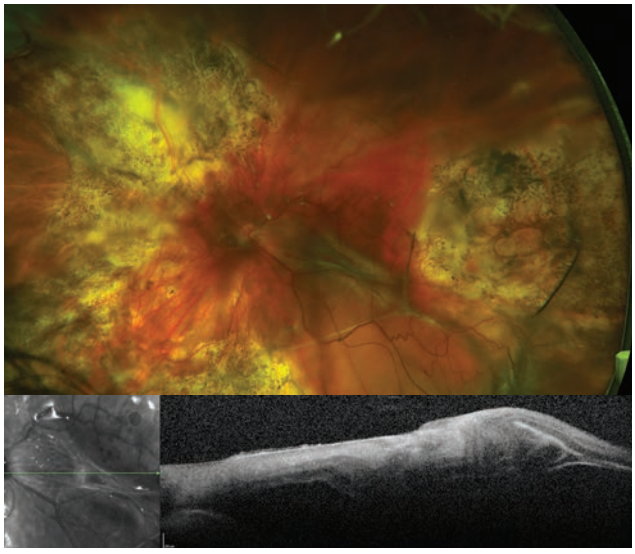


Figure 1. Preoperative view shows temporal retinal detachment with marked peripheral chorioretinal scarring, proliferative vitreoretinopathy, subretinal bands in the macula and a star fold with adjacent retinal break. Corresponding optical coherence tomography shows disorganized retinal laminations with tractional elevation.

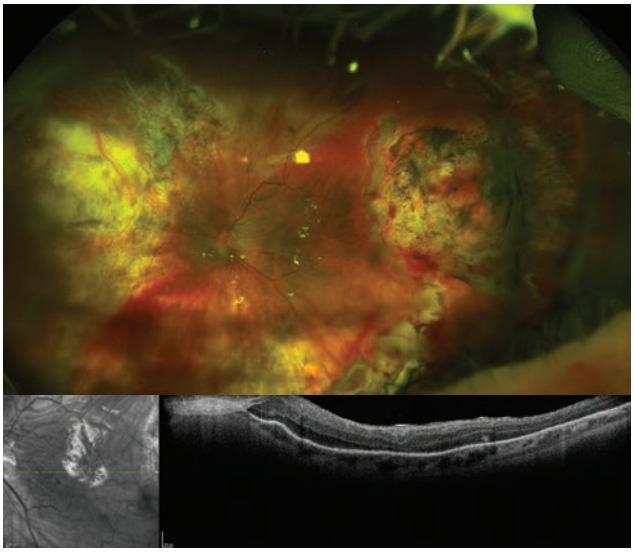


Figure 2. Postoperatively, the scleral buckle appears to support the area of inferior traction. Previous areas of macular proliferative vitreoretinopathy and subretinal bands have been released with no significant traction on the retina. Optical coherence tomography shows relief of macular traction with resolution of subretinal bands and fluid.

her visual acuity improved from bare light perception to 20/600 (aphakic). She expressed satisfaction with her decision to pursue a third surgical repair.

Discussion

Proliferative vitreoretinopathy is a common obstacle to retinal detachment surgery and accounts for approximately 75 percent of all surgical failures.[1,2] Controversy surrounds how to best manage PVR-related detachments. The decision is often based on surgeon preference and expertise.

Pars plana vitrectomy has gained popularity in recent years as a primary method of treating this difficult problem, with several studies showing promising visual and anatomic outcomes.[3,4] The use of scleral buckle is typically not employed in these instances because it has been thought to be more useful in cases with primarily anterior pathology.

However, our case demonstrates the utility of using a scleral buckle as an adjunct to vitrectomy to promote anatomical restoration by relieving retinal traction.

Yi Yao, MD, and colleagues in China presented a retrospective non-comparative study evaluating primary scleral buckling for patients with longstanding chronic RRD and subretinal fibrosis.[5] Of the 40 eyes studied, the mean duration of detachment was 13.8 months, and four eyes had documented PVR grade C or worse. Anatomical reattachment was achieved in 90 percent of eyes after one procedure and visual acuity improved to better than 5/100 in 77.5 percent of eyes after the final 24- month follow-up.

In a separate study, Philip Storey, MD, and the Wills PVR Study Group compared surgical treatment of 65 eyes at high risk for PVR (retinal detachment in two or more quadrants, retinal tears in one or more clock hour, preoperative PVR or vitreous hemorrhage) with PPV-scleral buckle vs. PPV alone.[6] The use of combined PPV-scleral buckle had higher surgical anatomical success relative to PPV alone. However, they found no appreciable difference in visual acuity at three months postoperatively.

In contrast, the European Vitreo-Retinal Society Retinal Detachment Study Group looked at reattachment rates for 637 eyes with grade C PVR RRD.[7] Higher anatomical failure rates were associated with combined scleral buckle-PPV (8.9 percent) compared to PPV alone (3 percent), although this result was not statistically significant.

(continued on page 18)

CLINICAL CONVERSATION
PROTOCOL U LESSONS FOR DME MANAGEMENT

Our expert panel explores insights about undertreatment and anatomical markers from the Phase II DRCRnet trial . Part 1 of 2.

Reported by Richard Mark Kirkner, Editor

Diabetic macular edema is increasing in prevalence and remains the most common cause of blindness among working-age populations in many countries. Retina specialists and their patients have been fortunate to have four Food and Drug Administration-approved agents available for the treatment of this disease, along with a fifth that is used extensively off-label.

Most retina specialists use intravitreal anti-VEGF injections as first-line management for diabetic macular edema, relegating intravitreal steroids to being second-line agents. Importantly, however, a clinically meaningful proportion of patients—32 to 66 percent[1]—will have persistent DME following at least six monthly intravitreal anti-VEGF injections.

About DRCRnet Protocol U

Protocol U of the Diabetic Retinopathy Clinical Research Network study was a Phase II trial that evaluated the effectiveness of the dexamethasone intravitreal implant (Ozurdex, Allergan) in combination with anti-VEGF therapy for treatment of persistent DME.[2,3] The study involved 129 eyes. Eligible patients had to receive at least three anti-VEGF injections within 20 weeks of study enrollment and have persistent diabetic macular edema with 20/32 or worse visual acuity.

At enrollment, patients were entered into a run-in phase in which they were treated with three monthly injections of ranibizumab (Lucentis, Roche/Genentech). If, after the run-in phase, the eye still met inclusion criteria, it was randomized into one of two treatment arms: ranibizumab; or ranibizumab plus dexamethasone at baseline, and

Clinical Conversation Expert Panel

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

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

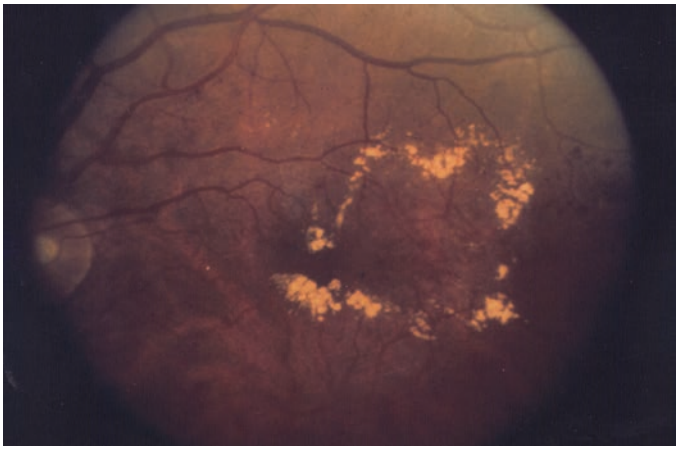
Michael Ober, MD, is a partner at Retina Consultants of Michigan in Southfield, and associate professor of ophthalmology at Oakland University, William Beaumont School of Medicine, Royal Oak, Mich. He is also an adjunct teaching professor at Henry Ford Health System, Detroit, and chief of staff at Straith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

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

then monthly visits with as-needed ranibizumab retreatment in both arms. The combination arm was eligible for a second dexamethasone implant beginning at month three. The primary outcome of Protocol U was change in mean visual acuity at six months.

In this Clinical Conversation, *Retina Specialist* Chief Medical Editor Charles C. Wykoff, MD, PhD, moderates a panel of experts discussing the findings of the Phase II Protocol U trial and their implications for clinical practice.

In this first of two parts, the panelists discuss what Protocol U reveals about appropriate treatment loads and the role of anatomic data in directing therapy. In the second part, to appear in the June issue of *Retina Specialist*, the panel will discuss specific strategies for using corticosteroids in the DME patient and how to manage side effects.



Diabetic macular edema pretreatment. National Eye Institute image

Do Physicians Undertreat Persistent DME?

Dr. Wykoff notes that, following the run-in phase of Protocol U, approximately one-third of eyes became ineligible for ultimate randomization into the core part of the trial because their persistent DME resolved. He asks, is that a reflection of the belief that in clinical practice, physicians are often undertreating persistent or active DME?

"There are two ways to look at that," says Michael Ober, MD. "The first is, there is a large percentage of under-treated patients, especially in the DME population; on average, these are younger patients. The second is that patients with DME take much longer to plateau in terms of visual and anatomic improvement. Studies suggest they may take five or six injections before they achieve the vast bulk of their improvements."

He notes that some of the patients in Protocol U had three or four injections within 20 weeks before their enrollment, and then had their next three or four injections in the run-in phase. "It may have taken that long for them to achieve the visual benefit and anatomic benefit," he adds.

Panelist Judy E. Kim, MD, notes that previous DRCRnet studies have shown that some patients are early, fast responders to treatment, and others are slow responders. "Some may require six or more monthly anti-VEGF injections before we see visual and/or anatomic improvement," she says.

At month six, the top-line Protocol U results showed no significant difference in visual acuity outcome between the two treatment arms, with mean improvements of 2.7 letters in the combination arm and 3 letters in the monotherapy arm.

However, anatomic outcomes did appear to differ between the arms, with the combination group having a significantly greater reduction in retinal thickness, with mean central subfield thickness decreases of 110 µm with combination therapy compared to 62 µm with monotherapy. Furthermore, 52 percent vs. 31 percent of patients in the combination vs. monotherapy arms had resolution of DME.

Correlating Anatomic, Visual Acuity Data

Dr. Wykoff asks the panelists how they correlate anatomic data with visual acuity. The consensus is that retinal thickness as a biomarker may not correlate well with visual acuity, although retinal dryness may.

In any study involving steroids, one has to normalize for cataract development, Dr. Ober says. "That certainly can skew the visual acuity data, even when you have equal or better anatomic outcomes," he says.

In addition, Dr. Ober notes that delayed initiation of the superior treatment regimen, especially with anti-VEGF therapy, can ultimately limit visual acuity potential. "The most pertinent example was in the

Take-home Point

In the first of two parts, this expert panel explores key lessons that Protocol U of the Diabetic Retinopathy Clinical Research Network study helped clarify. One is that retinal thickness may not correlate well with visual acuity, although retinal dryness may. The other is that emerging biomarkers may provide more precise insight into the course of the disease. The second part will appear in the June issue of *Retina Specialist.*

36-month results of the RIDE and RISE extension study,"[3] he says. "The initially sham-treated group received treatment in the crossover arm after 24 months." That same group had improvement in both vision and anatomy, but not at the same levels as the initially treated group.

"Identifying patients who are going to be slow responders to anti-VEGF alone is really the trick," adds Dr. Ober. "I don't think we have a way to do that yet."

Looking for New Biomarkers

Dr. Kim notes that multiple studies have shown that retinal thickness on optical coherence tomography correlates poorly with visual acuity. "Perhaps we have to look for other OCT biomarkers that may correlate better with visual acuity," she says.

Those biomarkers may include the integrity of the outer segment, the external limiting membrane and ellipsoid zone or other factors yet to be determined, she says. "Unlike exudative age-related macular degeneration, it appears that the retina can tolerate some fluid in DME," Dr. Kim says. "While a dry retina is the goal, many DME eyes had persistent edema, even though vision improved on maximal therapy."

Adds Michael A. Singer, MD, "We don't know exactly how OCT fits into visual acuity. There's definitely a disconnect." But that begs the question: What's the difference between visual acuity and visual function? "It's very hard to measure visual function," he says. "But when their OCT images show a dry macula, patients say they can do more activities of daily living."

Adds Dr. Ober, "We do need to look at more just retinal thickness." He notes that the integrity of the ellipsoid zone and outer photoreceptors is important, "but I would make a counterargument that the potential loss in ellipsoid-zone function may reflect permanent damage from the initial DME." RS

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RETINA ROUNDS

(Continued from page 15)

Our patient's case illustrates an application of scleral buckling to address posterior pathology in a manner that allows a contracted and PVR-affected retina to better adhere to the contour of the eye wall. Although retina surgeons often employ scleral buckling in younger or phakic patients to support anterior pathology,[8,9] our case and the cited literature demonstrate its potential utility in cases of severe PVR involving the posterior pole. Further prospective direct head-to-head comparative studies may be useful to determine the role of scleral buckling in such cases. RS

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HOW OCT ANGIOGRAPHY IS IMPROVING OUR VIEW OF DIABETIC RETINOPATHY

The data optical coherence tomography angiography obtains seem to correlate with the traditional clinical classification system of diabetic retinopathy.

By Steven S. Saraf, MD, and Kasra A. Rezaei, MD

The Early Treatment Diabetic Retinopathy Study (ETDRS) established and refined the current clinical grading of diabetic retinopathy that retina specialists use as an adaptation of the Modified Airlie House Classification. The parameters of the grading system rely primarily on identifying somewhat indirect signs of microvascular ischemic disease that include retinal hemorrhages, venous beading, intraretinal microvascular abnormalities or preretinal neovascularization.

However, identifying indirect signs of microvascular disease is fraught with challenges in ensuring reproducibility among different observers and operators, which may introduce error into research or clinical settings. ETDRS made attempts to measure and minimize this variability and found that certain exam features proved to be more reliable than others between independent observers.[1]

This is similar to what happened before the widespread use of optical coherence tomography to assess diabetic macular edema, when clinicians used biomicroscopy and they based the determination of clinically significant macular edema (CSME) on observed retinal thickening and presence of exudates as defined by ETDRS.

With the advent of OCT and anti-VEGF medications, a more direct approach has emerged. Clinicians can now easily identify macular fluid in cross-section and localize it in relation to the foveal center. They can also measure macular thickness to the nearest micron and easily establish trends between clinic visits.

Potent anti-VEGF agents allow more flexibility and salvage therapy if clinicians observe interval worsening much more rapidly than the previously applied focal/grid laser. In many ways, the enhanced visualization of microanatomy along with rapid advances in treatment have obviated the indirect measures of CSME as the ETDRS study had defined it.

Enter OCTA to Evaluate DR

There is now a growing body of literature applying the more nascent OCT angiography to the classification and management of diabetic retinopathy. Implementing OCTA to directly visualize diabetic microangiography in a far more detailed manner provides additional information about the severity of retinopathy not previously available in the classification scheme defined by ETDRS.

Going forward, understanding the applications of the additional information OCTA provides may similarly change our approach to diabetic retinopathy.

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DISCLOSURES: Drs. Saraf and Rezaei have reported no financial disclosures.

Basis of OCTA

OCT renders cross-sectional images of retinal tissues *in vivo*. The original basis of OCT was on time-domain technology that obtained depth-resolved tissue reflectivity characteristics based on the technique of interferometry. This approach takes light backscatter from the examined tissue and compares it to light reflected from a reference mirror. This can render the interference signal into cross-sectional images of the examined tissue once the position of the reference mirror is moved to detect backscattered light from varying depths.[2]

With technological advancements such as spectral domain and swept source OCT, methodologies that eliminate the need for movement of the reference mirror can detect backscattered signals from biological tissues and increase the acquisition speed. The use of a broader bandwidth light source in these approaches also considerably enhances axial resolution.

Now with improved speed and resolution, detailed three-dimensional images of the examined tissues can be created, allowing for detailed *in vivo* visualization of retinal and choroidal anatomy. However, the produced images do not differentiate between the static backscattering of light, such as those from the retinal laminations, compared to those that produce variable backscattering of light, such as in the retinal vasculature where varying configurations of red blood cells (RBCs) continually travel.[2]

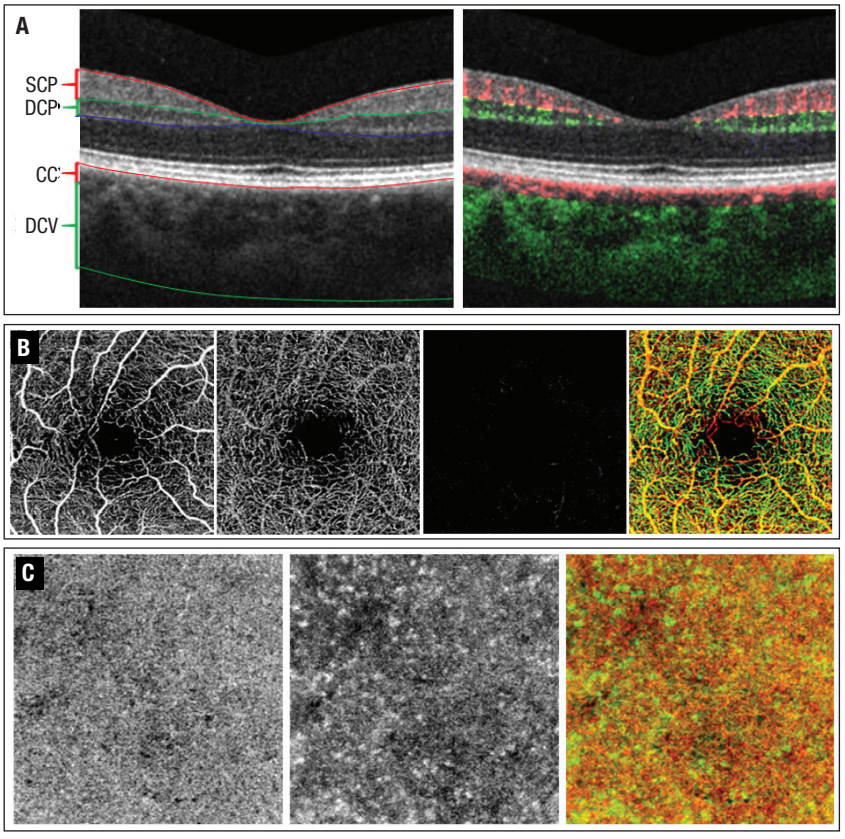

Figure 1. Optical coherence tomography angiography of a normal eye (A). Traditional structural OCT is shown next to a color-coded OCTA exhibiting areas of flow in the superficial (red, SCP) and deep (green, DCP) capillary plexuses as well as the choriocapillaris (red, CC) and deep choroidal layers (green, DCV). En face images of the retinal vasculature (B) show the superficial and deep capillary plexuses, both in isolation and in a combined image, as well as the avascular outer retina (black image). A combined image (C) shows the choriocapillaris and the outer choroidal vessels.

Isolating and exhibiting only tissues with variable backscattering of light is the basis of OCTA. By repeating an OCT scan multiple times within the same tissue, algorithms can be applied to isolate only areas that produce variable backscattering of light such as those produced by the continual flux of RBCs through blood vessels.

In the retina, the acquired image isolates functional blood vessels and has clinical applications in conditions that affect vascular tissues, such as DR, choroidal neovascularization,

Take-home Point

The clinical approach to diabetic retinopathy has changed rapidly with the advent of optical coherence tomography and anti-VEGF therapy. Now OCT angiography allows detailed visualization of capillary nonperfusion and neovascularization that may further enhance our approach to the care of diabetic patients. Current research has shown the additional information that OCTA obtains appears to correlate with the traditional clinical classification system of diabetic retinopathy. However, more research is needed to understand how to clinically apply the more quantitative and detailed information OCTA obtains and how to better personalize the management of diabetic retinopathy.

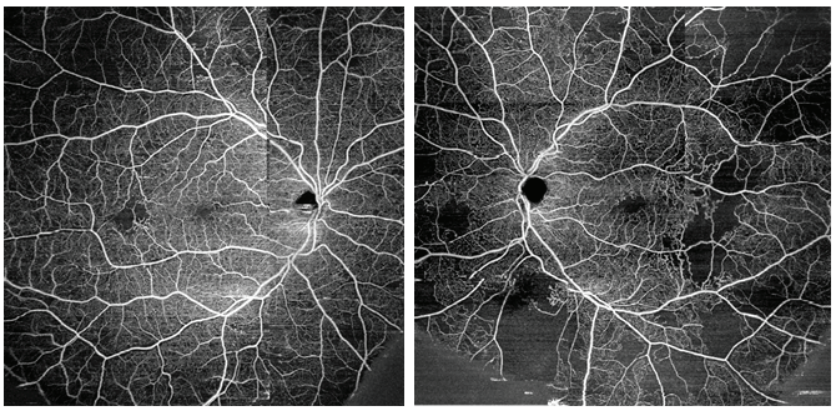

Figure 2. Widefield optical coherence tomography angiography of diabetic eyes without clinically apparent diabetic retinopathy. Despite no outward signs of retinopathy based on the Early Treatment Diabetic Retinopathy Study classification, the patient exhibits regions of capillary nonperfusion.

retinal vein occlusion, retinal artery occlusion or uveitis.[2]

Given that newer OCT technology can rapidly image tissues in a three-dimensional manner, the application of OCTA to these scans allows us to understand microvascular anatomy like never before. It can render pathology in greater detail.

Diseases that previously affected the "retinal circulation" or the "choroidal circulation" on conventional imaging, can now be further localized to the superficial or deep capillary plexuses of the retina or the choriocapillaris or deeper vessels of the choroid (*Figure 1, page 21*). Recalibrating our approach to conditions such as DR with this additional information will undoubtedly guide future research efforts.

Diabetes Without Clinically Apparent Retinopathy

The enhanced imaging of retinal capillaries using OCTA can enable the detection of DR even before clinical signs of mild nonproliferative diabetic retinopathy (NPDR) appear (*Figure 2*). Noriaki Takase, MD, and colleagues in Japan found that the foveal avascular zone was larger in both the superficial and deep capillary plexuses of diabetic patients with no clinical signs of diabetic retinopathy (NDR) compared to nondiabetic eyes.[3] Talisa de Carlo, MD, and colleagues at New England Eye Center corroborated these findings, and also found that the foveal avascular zone in NDR patients appeared remodeled (36 percent vs. 11 percent, p=0.01) and with higher rates of capillary nonperfusion (21 percent vs. 4 percent, p=0.03) compared to nondiabetic eyes.[4]

Another study quantified capillary vessel density in the superficial (44.35 percent vs. 51.39 percent, p=0.04) and deep (31.03 percent vs. 41.53 percent with, p<0.01) capillary plexuses, and was found to be less in NDR eyes compared to nondiabetic eyes.[5] Furthermore, systolic blood pressure and ocular perfusion pressure correlated significantly with deep capillary plexus density in NDR patients, but not in controls.

Authors have suggested that OCTA may be used in such circumstances to assess the risk of progression of NDR to clinically apparent DR, or even to screen patients for diabetes by observing these early microvascular alterations.

A pilot study has been performed implementing automated computer processing of OCTA images, which demonstrated 94.3 percent accuracy, 97.9 percent sensitivity and 87 percent specificity in detecting DR when analyzing the superficial and deep capillary plexuses.[6] The approach may have important implications in primary care and may

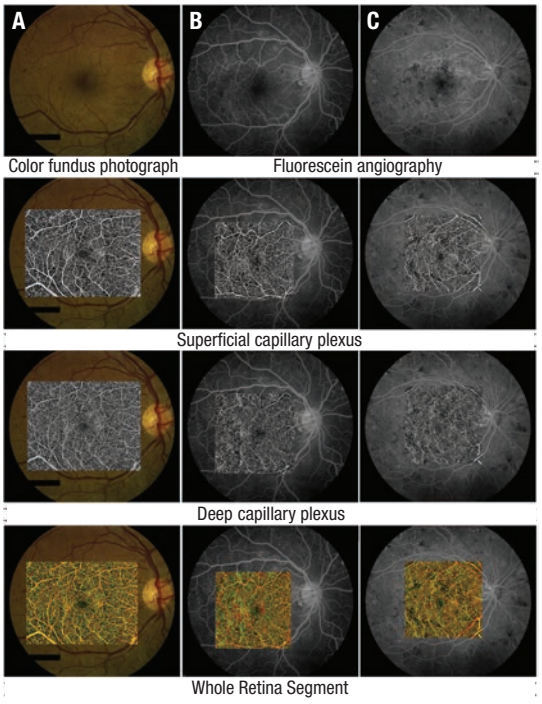

Figure 3. Optical coherence tomography angiography overlying traditional color fundus photography or fluorescein angiography in patients with mild (column A), moderate (B) and severe (C) diabetic retinopathy. The OCTA image reproduces capillary nonperfusion, microaneurysms, hemorrhages and other traditional features of diabetes without invasive fluorescein dye.

encourage further emphasis on preventative care.

NPDR

Clinicians can observe the traditional features of clinically apparent diabetic retinopathy with excellent detail using OCTA (*Figure 3*). However, OCTA also enables examination of DR features that were not previously accessible with traditional imaging modalities, and with far greater detail. For one, we can examine retinal perfusion with higher resolution and with better standardization than we can with fluorescein angiography.

This has allowed quantitative approaches to measure retinal perfusion that were not previously possible. Our group at the University of Washington, led by Alexander D. Lin, MD, calculated the capillary perfusion index, defined as percent coverage of functional retinal capillaries in the traditional ETDRS zones.[6]

We compared NDR/mild NPDR patients to moderate/severe NPDR patients. The results showed a significantly lower perfusion index in all non-foveal ETDRS zones in the moderate/severe NPDR group, suggesting a correlation between capillary perfusion and severity of diabetic retinopathy.

Kumar Sambhav, MD, and colleagues at the University of Florida College of Medicine, Jacksonville, reported similar results in a prospective cross-sectional study involving 102 eyes with newly diagnosed NPDR (36 mild NPDR, 21 moderate NPDR, 13 severe NPDR, and 32 with NPDR with DME) and 60 control eyes.[7]

They reported the following deep parafoveal vessel density measurements:

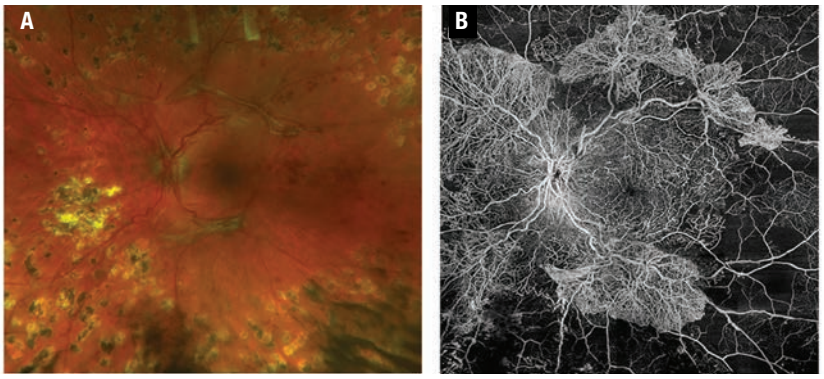

Figure 4. Fundus photograph (A) and widefield montage optical coherence tomography angiography (B) of nine 3-mm-by-3-mm scans exhibiting features of proliferative diabetic retinopathy with extensive neovascularization elsewhere and peripheral capillary nonperfusion.

- 25.23 percent in mild NPDR.
- 20.16 percent in moderate NPDR.
- 11.16 percent in severe NPDR.
- 17.91 percent in NPDR with DME.

Spearman correlation coefficient (rs) showed an inverse correlation between vessel density and NPDR severity in both the superficial (rs -0.87, p=0.083) and deep capillary plexuses (rs -0.96, p=0.017).[7]

Does OCT Enable More Quantitative Classification?

Given the observed correlations between clinically graded DR and capillary perfusion, it begs the question of whether OCTA may enable a more quantitative classification of DR that may allow for better predictions on progression to proliferative diabetic retinopathy, progression of macular ischemia or response to anti-VEGF therapy.

One study observed that eyes with both greater abnormality and more microaneurysms in the deep capillary plexus, along with larger foveal avascular zones, tended to respond less to anti-VEGF injections for DME than their counterparts.[8] Further study is needed to better understand and utilize data on retinal capillary perfusion in NPDR and possibly define quantitative classifications of severity based on OCTA imaging.

Proliferative DR

As in NPDR, the degree of retinal capillary perfusion has been correlated to the development of PDR. Peter Nesper, MD, and colleagues at Northwestern University performed an analysis and found linear correlations with the size of the foveal avascular zone, vessel density and percentage of area of nonperfusion. They did this comparing NPDR eyes to PDR eyes using 3-mm-by-3-mm scans centered on the fovea.[9] Dr. de Carlo and colleagues were able to create montage images (*similar to those in Figure 4*) using nine 3-mm-by-3-mm OCTA scans to observe the perfusion status of the retinal periphery.[10]

The Future of OCTA in DR

Future study is necessary to both standardize and elucidate the applications of widefield OCTA in DR, as the ischemic burden that contributes to the progression to PDR is likely more heavily concentrated in the

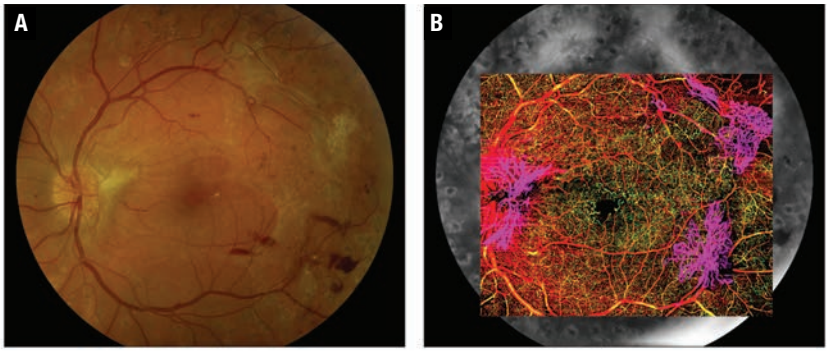

Figure 5: Color fundus photograph of a patient with proliferative diabetic retinopathy (A). Widefield optical coherence tomography angiography image overlying fluorescein angiography image of the same patient (B) exhibits pre-internal limiting membrane flow signals in pink, allowing for noninvasive monitoring of neovascularization of the disc and neovascularization of the retina elsewhere.

retinal periphery rather than the central macula.

OCTA can directly image the retinal neovascularization that results from capillary nonperfusion, including intraretinal microvascular abnormalities, neovascularization of the disc and neovascularization elsewhere (*Figure 5*).[11] Given that OCTA is noninvasive compared to traditional fluorescein angiography, routine monitoring of neovascular complexes is now possible and may become standard practice, especially as the evidence grows for the treatment of PDR with repeated anti-VEGF medications over traditional panretinal photocoagulation.[12–14]

Lastly, a growing body of evidence suggests that ocular involvement of diabetes may not be limited to the retina but may also affect the vasculature of the choroid. In one study involving 157 diabetic eyes, choroidal thickness on SS-OCT was on average thinner when compared to 71 normal eyes.[15] In another study, choroidal vascular density and volume were significantly reduced in PDR compared to NPDR and control eyes.[16]

Furthermore, choroidal vascular index—the ratio of the choroid composed of luminal vessel area to total choroidal area on the OCT scan—has been shown to be lower in diabetics compared to healthy controls when imaged with SS-OCT.[17] Dr. Nesper and his group used OCTA to show that choriocapillaris vessel density was significantly lower in PDR patients compared to NPDR and NDR patients.[9]

Another study used OCTA to observe flow voids in the choriocapillaris of 108 eyes of 66 consecutive diabetic patients, which the authors associated with higher severity of diabetic retinopathy and with poorer visual prognosis.[18] The role of assessing diabetic choroidopathy with OCTA remains to be seen. RS

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UVEITIS UPDATE: THE PARADIGM SHIFTS AGAIN

With new treatments on the verge of approval, here's a timely review of management strategies.

By Matthew A. Powers, MD, MBA, and Diana V. Do, MD

Uveitis is the cause of 10 to 15 percent of the overall cases of blindness in the United States,[1] and accounts for 30,000 new cases of legal blindness each year.[2] The incidence of uveitis has been calculated at 25 to 341 cases per 100,000 person years.[3-6] Among pediatric patients, males are affected more often than females. However, adult females are affected more than males.

The incidence of uveitis increases with age. Among patients younger than age 18 in the United States, the incidence is approximately 31 cases per 100,000 person years. That quadruples to 133 per 100,000 person years for patients age 18 to 64, and then almost doubles to 220 per 100,000 patient years for those age 65 and older.[7] Outside of tertiary care centers, anterior uveitis accounts for 92 percent of all cases.[8] Up to 50 percent of uveitis cases can be associated with an underlying systemic disease.[9]

In this clinical review, we provide a primer for retina specialists, because they may soon be playing a larger role in the management of uveitis as new drug treatments move toward approval.

Classification and Etiology

Multiple factors define uveitis. They are:[10]

- location;
- timing of onset;
- duration;
- course;
- laterality; and
- presence of granulomatous characteristics.

• *Location.* Anterior uveitis, consisting of iritis and iridocyclitis, is the most common form, accounting for 25 to 92 percent of cases.[11,12] Posterior uveitis, consisting of choroiditis, retinitis and chorioretinitis is the second most common, accounting for 5 to 38 percent of cases.[13] Intermediate uveitis is the third most common, accounting for 1 to 12 percent of cases.[2,11] Panuveitis is the least common, accounting for 1 to 9 percent of cases.[14]

• *Characteristics.* Uveitis etiology is divided accordingly:

- idiopathic;
- infectious;
- systemic inflammatory;
- hypersensitivity reactions; and
- uveitis syndromes restricted to the eye.

More than 90 percent of cases are noninfectious in nature.[7] About 9 percent of adult noninfectious causes are attributable to systemic

Take-home Point

The term uveitis refers to any inflammation of any structure along the uveal tract, including the anterior portion (iris and ciliary body) and the posterior portion (choroid). The inflammation may be primarily located in the uvea, or it may be a consequence of spillover of adjacent inflammation. Uveitis is a complex clinical entity composed of many diseases and management options. This article reviews the etiology, clinical workup and treatments, including emerging therapies. Each case is different, and clinicians must carefully consider those differences to minimize the risk of serious vision loss.

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Disclosures: Dr. Do is a consultant to Santen, Genentech and Bayer Healthcare Pharmaceuticals. Dr. Powers had no relationships to disclose

immune conditions.[8]

In the United States, most infectious causes of uveitis are decreasing,[14] although in many developed counties syphilis has been increasing in prevalence in recent years.[15] In anterior uveitis, the most common causes are idiopathic, seronegative spondyloarthropathies, juvenile idiopathic arthritis (JIA) and herpetic disease.[16] The most common cause of posterior uveitis is toxoplasmosis.[17] Panuveitis is typically idiopathic or due to sarcoidosis, whereas intermediate uveitis is typically idiopathic.[12] A comprehensive list of etiologies appears in Table 1.

Workup Step One: History

A detailed history is crucial during the workup of uveitis. Key components are evaluation of symptoms, investigation of medical, social and family histories, and a review of systems.

• *Evaluation of symptoms.* Symptoms alone can often determine anatomic classification. Symptoms of acute anterior uveitis typically include pain, redness, photophobia and blurry vision. In a chronic case, anterior uveitis may present with minimal pain and photophobia. Intermediate and posterior uveitis typically present with floaters or blurry vision.

Inquire about symptom

Table 1. Uveitis Etiology and Systemic Characteristics

Etiology	Systemic Features
Acute Anterior Uveitis	
Behçet's syndrome	Oral/genital ulcers, erythema nodosum
Glaucomatocyclitic crisis (Posner–Schlossman syndrome)	NA
Herpetic/viral (herpes simplex virus, varicella zoster virus, cytomegalovirus)	Vesicular lesions (herpes simplex, varicella zoster viruses)
Kawasaki disease	Fever, conjunctivitis, strawberry tongue, skin erythema
Post-streptococcal	Preceding streptococcal infection
Relapsing polychondritis	Auricular, nasal, laryngotracheal chondritis
Seronegative spondyloarthropathies	Back pain, ankylosing spondylitis, reactive arthritis
Tubulointerstitial nephritis and uveitis syndrome	NA
Fuchs' heterochromic iridocyclitis	NA
Juvenile idiopathic arthritis	Oligoarthritis
Sarcoidosis	Dyspnea, erythema nodosum, skin nodules
Syphilis	Rash on palms and soles, chancres, gummas
Tuberculosis	Fevers, night sweats, cough, weight loss
Intermediate Uveitis	
Lyme disease	Erythema migrans, headache, musculoskeletal pain
Multiple sclerosis	Numbness, weakness, optic neuritis
Sarcoidosis	Dyspnea, erythema nodosum, skin nodules
Posterior Uveitis	
Birdshot chorioretinopathy	NA
Cat-scratch disease	Malaise, headache
Multifocal choroiditis/panuveitis	NA
Presumed ocular histoplasmosis syndrome	NA
Sarcoidosis	Dyspnea, erythema nodosum, skin nodules
Serpiginous chorioretinopathy	NA
Syphilis	Rash on palms and soles, chancres, gummas
Toxocariasis	NA
Toxoplasmosis	NA
Tuberculosis	Fevers, night sweats, cough, weight loss
Viral (herpes simplex virus, varicella zoster virus, cytomegalovirus)	Vesicular lesions (herpes simplex, varicella zoster viruses), immunocompromise (cytomegalovirus, progressive outer retinal necrosis)
West-Nile virus	Headache, myalgia, arthralgia, gastrointestinal symptoms, rash
Panuveitis	
Endophthalmitis	If endogenous, symptoms of primary infection
Sarcoidosis	Dyspnea, erythema nodosum, skin nodules
Sympathetic ophthalmia	Trauma history
Syphilis	Rash on palms and soles, chancres, gummas
Toxocariasis	NA
Toxoplasmosis	NA
Tuberculosis	Fevers, night sweats, cough, weight loss
Vogt-Koyanagi-Harada disease	Hearing loss, tinnitus, fever, headache, neck stiffness, vitiligo, poliosis

Table 2. Symptoms Patients May Fail to Report

- Fever
- Weight loss
- Malaise
- Night sweats
- Arthralgias
- Back pain
- Joint stiffness
- Tinnitus
- Headache
- Neck stiffness
- Paresthesias
- Weakness
- Altered mental status
- Rashes
- Sores
- Hair loss
- Vitiligo
- Poliosis
- Insect bites
- Shortness of breath
- Cough
- Oral ulcers
- Dysuria
- Genital ulcers
- Diarrhea or bloody stools

course, laterality, previous episodes, response to treatment and any associated systemic symptoms.

• *Medical and surgical history.* Carefully review prior episodes of trauma, as well as medical and surgical history. Medical history should focus on systemic diseases such as sarcoidosis, JIA, HIV/AIDS, tuberculosis and syphilis. Medication use may be important.

• *Social history.* This investigation should focus on race/ethnicity, birthplace, travel history, diet, sexual history and history of intravenous drug use.

• *Family history.* This should involve family history of systemic or ocular diseases, contagious diseases and prenatal infections.

• *Review of systems.* This final step may reveal symptoms that the patient neglected to report. Table 2 lists items to inquire about.

Conducting the Examination

A careful ophthalmic examination will help to localize the inflammation and may provide clues to the etiology of the disease. Intraocular pressure is usually reduced in acute anterior uveitis due to ciliary body shutdown. Ciliary body atrophy or detachment can occur in chronic cases, which can produce chronic hypotony and eventually phthisis.

Elevated IOP may also result from trabeculitis, inflammatory plugging of the trabecular meshwork, pupillary block, peripheral anterior synechiae or a steroid response. Elevated IOP is particularly associated with herpetic anterior uveitis.[16]

The examination should focus on the following anatomical regions:

• *Conjunctiva.* Inspect this structure for nodules (especially in sarcoidosis) or ciliary flush (perilimbal injection), which may appear in anterior uveitis. Conjunctival nodules can be biopsied in cases where the diagnosis is uncertain.

• *Cornea.* The cornea may also display epithelial dendrites, ulcers or stromal inflammation in herpetic disease. Keratic precipitates (KPs)—collections of inflammatory cells—may be present on the corneal endothelial surface. They are typically white in appearance early on and can later become more pigmented. Fuchs' heterochromic iridocyclitis and herpetic uveitis can produce KPs outside of Arlt's triangle.

Band keratopathy may also be present in chronic uveitis. Non-granulomatous disease will manifest small white KPs, while larger, "mutton-fat" KPs are more prevalent in granulomatous uveitis. The granulomatous distinction may be helpful, because a select number of diseases are classified as such. They include TB, cat-scratch disease, sarcoidosis, syphilis, Lyme disease and some cases of herpetic uveitis.

• *Anterior chamber.* In the anterior chamber, cells (leukocytes) and flare (protein) can appear in the aqueous humor. In severe cases, fibrin or a hypopyon may be present.

Persistent flare, which does not resolve with treatment, can be seen in long-standing uveitis. The presence of flare may predispose a patient to synechiae, which can lead to angle-closure glaucoma if pupillary block develops.

Within the iris, sectoral atrophy may be present in herpetic disease. In granulomatous disease, the iris may display nodules at the pupillary margin (Koeppe), within the stroma (Busacca) or in the angle (Berlin).

• *Lens.* Cataracts can occur either from longstanding inflammation or prolonged use of corticosteroids. Usually, they are of the posterior subcapsular type, but they may also be cortical.

• *Posterior segment.* The retina, optic nerve and choroid can display varying signs of inflammation. The optic nerve head may develop edema. The vessels may display vascular sheathing or hemorrhages, and retinal edema or necrosis will cause whitening.

Atrophy can develop after inflammation resolves and may predispose the eye to retinal breaks and detachments. Deep to the retina, creamy yellow lesions can represent choroidal infiltration. If Bruch's membrane is broken, choroidal neovascularization may develop.

Within the vitreous cavity, vitritis, snowballs (especially suggestive of sarcoidosis and intermediate uve-

Table 3. Laboratory Testing and Other Studies for Uveitis

Etiology	Laboratory Studies	Other Studies
Acute Anterior Uveitis		
Behçet's syndrome	HLA-B51	NA
Glaucomatocyclitic crisis (Posner–Schlossman syndrome)	Aqueous fluid PCR for viral cause	NA
Herpetic/viral (herpes simplex virus, varicella zoster virus, cytomegalovirus)	Aqueous fluid PCR	NA
Kawasaki disease	NA	EKG, TTE
Post-streptococcal	Anti-streptolysin-O titer	NA
Relapsing polychondritis	NA	NA
Seronegative spondyloarthropathies	HLA-B27	Sacroiliac films
Tubulointerstitial nephritis and uveitis syndrome	Serum BUN and creatinine, urine ß2 microglobulin	Urinalysis
Chronic Anterior Uveitis		
Fuchs' heterochromic iridocyclitis	NA	NA
Herpetic/viral	Aqueous fluid PCR	NA
Juvenile idiopathic arthritis	Antinuclear antibodies	NA
Sarcoidosis	ACE, lysozyme	Chest X-ray, chest CT
Syphilis	RPR, FTA-ABS, CSF analysis	NA
Tuberculosis	PPD, quantiferon	Chest X-ray
Intermediate Uveitis		
Lyme disease	ELISA or western blot	NA
Multiple sclerosis	CSF analysis	Brain MRI
Sarcoidosis	Chest X-ray, ACE, lysozyme	Chest X-ray, chest CT
Posterior Uveitis		
Birdshot chorioretinopathy	HLA-A29	FA, ICGA, FAF, ERG, OCT
Cat-scratch disease	Bartonella serology	FA
Multifocal choroiditis/panuveitis	NA	FA, ICGA, FAF, OCT
Presumed ocular histoplasmosis syndrome	NA	FA, ICGA, FAF, OCT
Sarcoidosis	Chest X-ray, ACE, lysozyme	Chest X-ray, chest CT
Serpiginous chorioretinopathy	NA	FA, ICGA, FAF, OCT
Syphilis	RPR, FTA-ABS, CSF analysis	NA
Toxocariasis	NA	NA
Toxoplasmosis	IgG serology, aqueous PCR	NA
Tuberculosis	PPD, quantiferon	Chest X-ray
Viral (herpes simplex virus, varicella zoster virus, cytomegalovirus)	Aqueous or vitreous PCR	NA
West-Nile virus	IgM serology, CSF analysis	FA, ICGA
Panuveitis		
Endophthalmitis	Vitreous culture, blood culture	NA
Sarcoidosis	Chest X-ray, ACE, lysozyme	Chest X-ray, chest CT
Sympathetic ophthalmia	NA	FA, US, OCT with EDI
Syphilis	RPR, FTA-ABS, CSF analysis	NA
Toxocariasis	NA	NA
Toxoplasmosis	IgG serology, aqueous PCR	NA
Tuberculosis	PPD, quantiferon	Chest X-ray
Vogt-Koyanagi-Harada disease	CSF pleocytosis	FA, US, OCT with EDI

Key: ACE—Angiotensin converting enzyme; BUN–Blood urea nitrogen; CSF–Cerebrospinal fluid; CT—Computed tomography; EDI–Enhanced depth imaging; EKG–Electrocardiogram; ERG–Electroretinogram; ELISA–Enzyme-linked immunosorbent assay; FA–Fluorescein angiography; FAF–Fundus autofluorescence; FTA-ABS–Fluorescent treponemal antibody absorption; ICGA–Indocyanine green angiography; MRI–Magnetic resonance imaging; OCT–Optical coherence tomography; PCR–Polymerase chain reaction; PPD–Purified protein derivative; RPR–Rapid plasma regain; TTE–Transthoracic echocardiogram; US—Ultrasound.

itis),[18] fibrosis or cyclitic membranes may be present. The location of white cells in the vitreous can help pinpoint the source of inflammation. In iridocyclitis, cells are located more anteriorly, while in intermediate or posterior uveitis, cells are more distributed or appear posteriorly. Snowbanking overlying the ora serrata can occasionally occur.

Differential Diagnosis

Classification can help to rapidly narrow the differential diagnosis. While much overlap occurs, many etiologies are strongly linked to certain uveitis classes. For example, HLA-B27 positivity is characteristic of acute anterior uveitis, whereas toxoplasmosis is associated with a posterior uveitis. Along with the classification of uveitis, other important clues to the differential include ethnicity and exposure history. Table 1 (*page 26*) provides a breakdown of classifications and their associated differentials with systemic findings.

Lab Testing and Imaging

- *Laboratory testing.* Tailor lab

testing to the clinical situation. Most cases of unilateral, nongranulomatous anterior uveitis do not need a laboratory workup. More complex situations may require testing tailored to the patient. Table 3 lists recommended laboratory tests for the different suspected etiologies of uveitis.

The most appropriate way to approach laboratory testing is to form a differential diagnosis and then customize the testing accordingly. However, nearly every lab panel for uveitis should include testing for syphilis, sarcoidosis and TB.[16]

• *Imaging.* Testing can also include optical coherence tomography to evaluate for cystoid macular edema and choroidal thickness if enhanced depth imaging is available (*Figure 1*); fluorescein angiography to assess for vascular leakage and serous retinal detachments; and ultrasonography to evaluate for posterior scleritis. Another option is scanning laser ophthalmoscopy (*Figure 2*).

Systemic imaging, such as chest X-ray and CT scan, can be helpful when sarcoidosis is suspected. In cases unresponsive to treatment or in which infectious or neoplastic causes are suspected, diagnostic vitrectomy or chorioretinal biopsy may help increase diagnostic certainty.

Treatment for Uveitis

The primary goal of treatment in uveitis is to reduce inflammation and preserve sight. This often requires either antimicrobial or immunomodulatory agents.

• *Corticosteroids.* These agents are first-line therapy in most cases of noninfectious uveitis and are especially helpful in anterior uveitis.

The rule of thumb is to use the safest, most potent agent (*Table 4, page 30*). Most clinicians start with prednisolone acetate. Assess IOPs in any patient on topical steroids at least two weeks after beginning the steroid. Monitor any patient with a history of steroid response closely.

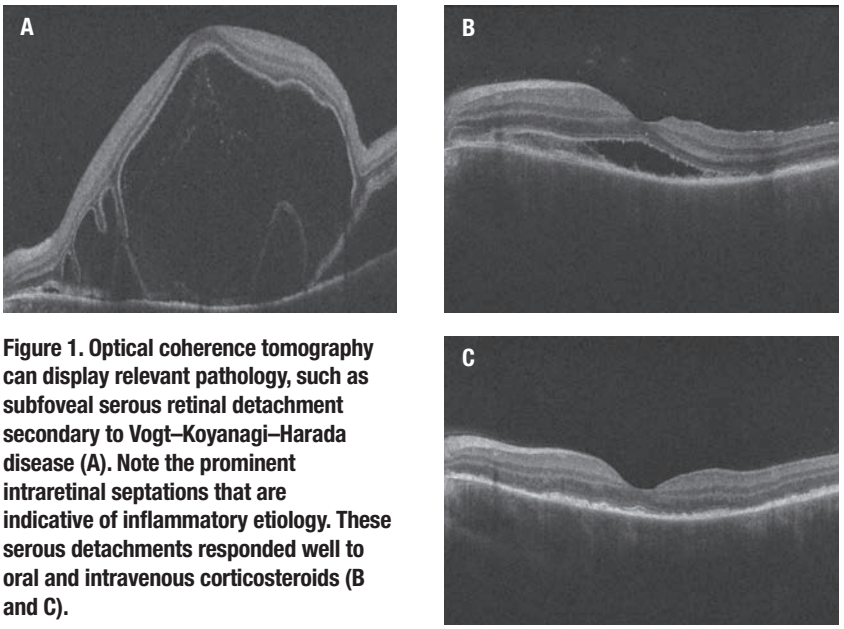

Figure 1. Optical coherence tomography can display relevant pathology, such as subfoveal serous retinal detachment secondary to Vogt–Koyanagi–Harada disease (A). Note the prominent intraretinal septations that are indicative of inflammatory etiology. These serous detachments responded well to oral and intravenous corticosteroids (B and C).

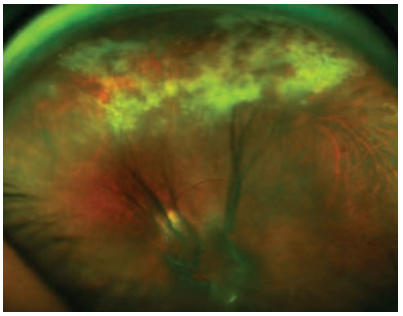

Figure 2. Scanning laser ophthalmoscopy displays cytomegalovirus retinitis of the left eye. Note the vitreous opacities and white granular appearance of the retinitis superiorly without hemorrhages, which are classically seen in this condition.

• *Alternatives to topical steroids.* For patients that cannot tolerate topical steroids, triamcinolone can be injected into the sub-Tenon's space. This can be given every month and titrated to patient response. Triamcinolone can also be administered intravitreally and should last weeks to months.

Another intravitreal option is the dexamethasone degradable implant (Ozurdex, Allergan), which lasts one to three months. A fluorocinolone acetonide-sustained release device (Retisert, Bausch + Lomb) can be sutured at the pars plana; it lasts 2.5 to three years.

In cases that involve anterior inflammation, a cycloplegic will also prevent ciliary spasm and help ameliorate photophobia. In addition, movement and deepening of the iris help to prevent the formation of posterior and anterior synechiae.

• *Systemic corticosteroids.* Severe uveitis of any location or posterior uveitis may warrant oral or intravenous corticosteroids. The typical dose of oral prednisone starts at 1 mg/kg (maximum 60 mg/day), while intravenous methylprednisolone starts at 1 gr/day for three days and is then followed with an oral prednisone taper.

Any patient on more than two weeks of systemic steroids requires

Table 4. Potency Of Topical Corticosteroids

In descending order, the strongest topical steroids are:

- Difluprednate (Durezol, Novartis)
- Prednisolone acetate*
- Prednisolone sodium phosphate*
- Rimexolone (Vexol, Alcon; discontinued in United States)
- Loteprednol etabonate (Alrex, Bausch + Lomb)
- Fluoromethalone*

* generic

a taper. Patients should never stay on a dose greater than 7.5 to 10 mg per day chronically. Patients on long-term therapy should also receive calcium and vitamin D supplementation.

• *Immunomodulatory agents.* If corticosteroids do not achieve control, immunomodulatory agents are an option. Locally, sirolimus has shown promise as a bimonthly intravitreal therapy. Phase I data showed good control, and the SAVE trial showed it reduced vitreous haze and the need for corticosteroid therapy. The SAKURA study demonstrated that sirolimus reduced ocular inflammation and increased the probability of tapering steroids.[19–21]

Systemic Therapy

If local immunomodulatory control is inadequate, the patient may need systemic treatment. Clinicians who are not comfortable using these medications should refer the patient to a uveitis specialist or rheumatologist. Limited data exist, and most providers will base medication choice on familiarity, side-effect profile and comorbidities.

• *Antimetabolites.* These agents include methotrexate, mycophenolate and azathioprine. If greater control is needed, another antimetabolite or drug from a new class can be added. Adalimumab (Humira, Abbvie), a biologic tumor necrosis factor-alpha inhibitor, is approved for noninfectious intermediate, posterior and panuveitis.[22]

• *Alkylating agents.* If a combination of classes cannot control the disease, an alkylating agent may be needed. This class carries significant side effects, namely the risk of sterility, bone marrow suppression and increased risk of malignancy.

Visual Prognosis

The visual prognosis for uveitis varies widely based on location. The chances of a 25-percent decrease in visual acuity, based on location, are as follows:[23]

- anterior uveitis, 1 to 4 percent;
- posterior uveitis, 43 percent;
- intermediate uveitis, 66 percent; and
- panuveitis, 40 percent.

CME followed by cataract and glaucoma causes visual impairment or blindness in up to 35 percent of patients.[9,24]

Despite which specialist manages the medical therapy, the ophthalmologist plays a vital role in monitoring these patients and treating ocular complications such as ocular hypertension, CME, retinal detachments, hypotony and cyclitic membranes.

Clinicians who carefully consider the presenting signs and symptoms of uveitis, examination findings, differential diagnosis and treatment options are well-positioned to adequately manage the disease and preserve sight.

Even with good control, both uveitis patients and clinicians must remain watchful for recurrences to prevent irreversible damage. Due to the expanding armamentarium of therapeutic options, many uveitis patients can achieve excellent control of inflammation and have minimal ocular and systemic side effects. RS

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PIPELINE UPDATE
WHAT'S EXPECTED TO EMERGE IN 2018

Here's a look at no fewer than 19 agents for AMD and DME expected to reach important milestones in the next 12 months.

By Richard Mark Kirkner, Editor

Development of new treatments for age-related macular degeneration and diabetic macular edema often overlaps, as multiple drug developers pursue parallel courses for both indications. Here, we provide snapshots of drugs that are in clinical trials and are either on track to reach important milestones this year or next, or have been sidetracked by disappointing clinical trial readouts. This list has been compiled with the help of Editorial Board Member Emmett T. Cunningham, MD, PhD, and is based on presentations at the Ophthalmology Innovation Summit and our own research and verification.

Age-related Macular Degeneration

Eylea (Regeneron Pharmaceuticals). Regeneron is on track to get Food and Drug Administration approval of 12-week dosing of aflibercept (Eylea) by the summer of this year. In December, the FDA issued a Prescription Drug User Fee Act date of August 11, 2018, for the 12-week dosing. That's tantamount to a deadline date for a decision.

The supplemental Biologics License Application the FDA accepted for review is based on an analysis of two-year results from the pivotal VIEW 1 and VIEW 2 trials that showed 51 percent of study patients had their aflibercept dosing interval extended to every 12 weeks at the beginning of the second year (week 52) of treatment, based on an evaluate-and-extend approach.[1] They maintained the 12-week dosing interval and best-corrected visual acuity gains at two years without any new safety issues. Criteria for 12-week dosing include physician recommendation and no evidence of new or progressive wet AMD.

Brolucizumab (Novartis). This humanized monoclonal antibody, also known as RTH258, targets vascular endothelial growth factor-A. At the American Academy of Ophthalmology Retina Subspecialty Day last year, Pravin Dugel, MD, reported results of the Phase III HAWK and HARRIER head-to-head trials comparing brolucizumab and aflibercept.[2]

At week 16, 35 percent fewer brolucizumab 6-mg patients had intraretinal fluid (IRF) and/or subretinal fluid (SRF) in HAWK, and 33 percent fewer in HARRIER ($p<0.0001$ for both).[2]

At week 48, 31 percent fewer patients on brolucizumab 6-mg had IRF and/or SRF in HAWK and 41 percent fewer in HARRIER ($p<0.0001$ for both). The brolucizumab 6-mg group also demonstrated superior reductions in central subfield thickness. Jefferies' analyst Jeffrey Holford predicted a launch of RTH258 in the United States next year and projected peak sales of $2 billion if it also gets FDA approval for DME.

Take-home Point

Clinical trials of a host of investigative treatments for age-related macular degeneration and diabetic macular edema are expected to provide either final results or readouts in 2018. A few are further along in the pipeline. Approval may come for a 12-week dosing of aflibercept (Eylea, Regeneron). Brolucizumab (RTH258, Novartis) may get approval in the next two years. But the pipeline doesn't flow for everyone: No fewer than two development programs have already been halted.

TABLE. Age-related Macular Degeneration and Diabetic Macular Edema Pipeline

Agent name	Description/Active Ingredient	Company	Most Recent Milestone	What's Next
Wet AMD				
Brolucizumab	RTH258 humanized single-chain antibody fragment (scFv)	Novartis	Phase III results reported 2017	Expected FDA approval 2019-2020
DE-122	Carotuzimab	Santen	Top-line Phase I/II results reported February 2018	
Eylea	Aflibercept	Regeneron Pharmaceuticals	FDA accepted supplemental application for 12-week dosing	Prescription Drug User Fee Act date August 11, 2018
GB-102	Sustained-release sunitinib (pan VEGFR antagonist)	Graybug Vision	Phase Ib/IIa "switching" study ongoing	Top-line data due 1H 2018
ICON-1	Anti-tissue factor fusion protein	Iconic Therapeutics	Phase IIa EMERGE trial results reported February 2018	Moving to Phase IIb later in year
Nesvacumab	Anti-angiopoietin-2 antibody	Regeneron	Phase IIb ONYX trial results for wet AMD and RUBY for DME reported	Decision made to not pursue Phase III trial
OHR	Topical squalamine lactate 2%	Ohr Pharmaceuticals	Top-line MAKO trial results reported January 2018	Development program discontinued
PAN-90806	Topical selective anti-VEGFR	PanOptica	Phase I/II trial commenced 2016	Data expected 1H 2019
RG7716	Anti-angiopoietin-2 bispecific antibody	Roche/Genentech	Phase II AVENUE and STAIRWAY trials for wet AMD ongoing; Phase II BOULEVARD results for DME reported February 2018	AVENUE data expected later 2018. FDA Discussions on Phase III to start after data assessment.
RPDS	Ranibizumab port delivery system	Roche/Genentech	Phase IIb fully enrolled	Final data collection expected Q2 2018.
X-82	Oral anti-VEGF agent	Tyrogenex	Phase II trial completed enrollment March 2017	Phase IIb results due 2Q 2018
Zimura	Avacincaptad pegol	Ophthotech Corporation	Dose-ranging, open-label Phase IIa trial ongoing	Readout of top-line Phase IIa data expected by yearend 2018.
Dry AMD/Geographic Atrophy				
APL-2	Complement C3 inhibitor	Apellis Pharmaceuticals	18-month Phase II FILLY results reported February 2018	Phase III to start 2H 2018
RG7417	Lampalizumab	Roche/Genentech	Removed from Phase III trial February 2018	Development program discontinued
Zimura	Avacincaptad pegol	Ophthotech Corporation	Phase IIb trial ongoing	Readout of top-line Phase IIb data expected 2H 2019.
DME				
AKB-9778	Small-molecule Tie-2 Activator	Aerpio Therapeutics	TIME Phase IIb trial completed enrollment in February	Data due 2Q 2019
Luminate	Anti-integrin	Allegro Ophthalmics	Subgroup analysis of Phase IIb DEL MAR results under way	Phase III to be initiated 2018
OPT-302	"Trap" mechanism targets VEGF-C and VEGF-D	Ophthea	Phase Ib/IIa trial initiated in January 2018	Primary analysis expected in 1H 2019

Carotuximab (Santen). Top-line results from the Phase I/II study of DE-122 (carotuximab) for refractory wet AMD were presented last month at Bascom Palmer Eye Institute's 15th annual Angiogenesis, Exudation and Degeneration meeting. Victor H. Gonzalez, MD, study investigator and founder of Valley Retina Institute in McAllen, Texas, reported no serious adverse events. [3]

Carotuximab is a novel antibody to endoglin, a protein over-expressed on endothelium essential for angiogenesis and upregulated by anti-VEGF.

DE-122, a novel ophthalmic formulation of carotuximab, was active in preclinical choroidal neovascularization models and may enhance the effect of anti-VEGF agents.

A Phase IIa randomized-controlled trial is assessing the efficacy and safety of intravitreal injections in combination with ranibizumab (Lucentis, Roche/Genentech) compared to ranibizumab monotherapy in patients with wet AMD. The results so far have also suggested bioactivity of DE-122 in refractory wet AMD patients, as measured by mean change in central retinal subfield thickness based on spectral-domain optical coherence tomography.

GB-102 (Graybug Vision). Graybug expects an initial readout of top-line Phase Ia/IIb results of GB-102 for treatment of wet AMD in the first half of the year. GB-102 is an injectable formulation of sunitinib, a tyrosine kinase inhibitor that blocks multiple VEGFR pathways. The goal is to reduce treatments for wet AMD, DME and retinal vein occlusion to once or twice a year, President and CEO Jeff Cleland, PhD, reported at the Ophthalmology Innovation Summit last November.

The two-part ADAGIO trial is evaluating patients with wet AMD who are already on anti-VEGF agents and are then switched over to treatment with GB-102 alone. The company expects a preliminary readout on the safety and efficacy of the Phase I trial in the fourth quarter this year, with Phase II top-line safety and efficacy results due in 2020.

X-82 (Tyrogenex). Tyrogenex expects to report Phase II results of this oral candidate for treatment of wet AMD this year. The trial completed enrollment in March 2017 and is evaluating treatment with one of three doses of X-82 (vorolanib) or placebo after 52 weeks. The trial exceeded its enrollment target of 132 patients by 25 patients, senior VP and development director Daniel Salazar, PhD, reported last March.

RG7716 (Roche/Genentech). RG7716 is the subject of The STAIRWAY trial, which is expected to complete data collection in June. RG7716 is a novel anti-VEGF-A and anti-angiopoietin-2 (Ang-2) bispecific, monoclonal agent. It simultaneously binds to and inactivates VEGF-A and Ang-2.

The Phase II AVENUE study of RG7716 for wet AMD was due for completion in January with final data collection in September. Data from the BOULEVARD trial, which is investigating RG7716 in patients with diabetic macular edema, was presented at the Angiogenesis meeting. (*See page 35 for a more detailed discussion of the DME program.*)

RPDS (Roche/Genentech). RPDS stands for ranibizumab port delivery system. Genentech is developing the port to deliver ranibizumab (Lucentis) over a period of months, potentially reducing the burden of frequent injections. The RPDS is placed beneath the conjunctiva, and is refillable by injection.

The primary endpoint of the LADDER trial is time until a participant first requires an implant refill. Final data collection is estimated for September 2018. Genentech's parent, Roche, acquired ForeSight Vision 4, which had been developing the port system, in 2017. The companies had been collaborating on RPDS since 2010.

Squalamine (Ohr Pharmaceutical). Research into new drugs is fraught with risk, as Ohr Pharmaceutical found out. The company had much hope for its topically administered squalamine in combination with monthly ranibizumab for treatment of wet AMD. However, Ohr discontinued development of the agent after disclosing the MAKO study failed to meet its primary endpoint—mean visual acuity gain at nine months. (*See "Two Drug Development Programs Halted," News, page 9*).

Dry AMD/Geographic Atrophy

APL-2 (Apellis Pharmaceuticals). Apellis Pharmaceuticals reported 18-month results of the FILLY trial of APL-2, a complement C3 inhibitor, in patients with AMD-related geographic atrophy.[4] Reporting at the Macula Society meeting last month, Rishi Singh, MD, of the Cole Eye Institute at the Cleveland Clinic, said 18-month outcomes mirrored 12-month results that showed monthly intravitreal APL-2 resulted in a 29-percent reduction in the rate of GA lesion growth compared to sham (p=0.008). Every-other-month administration of APL-2 resulted in a 20-percent reduction in GA lesions (p=0.067). The Phase III trial is scheduled to begin in the second half of this year.

Zimura (Ophthotech Corporation). Last year Ophthotech Corporation moved up the time line to obtain top-line data from its ongoing Phase II/III trial of Zimura (avacincaptad pegol) monotherapy in GA by reducing the number of patients, shortening the time point for attaining the primary efficacy endpoint and reducing study costs. The modified study design incorporated patients already enrolled. Zimura targets and inhibits the complement protein C5 in the complement cascade.

Ophthotech is pursuing other Zimura programs. It has started an open-label Phase IIa trial of Zimura in combination with ranibizumab

(Continued on page 35)

By Paul Hahn, MD, PhD »

Endoillumination Without an Assistant

A technique to perform peripheral vitreoretinal surgery with chandelier endoillumination independently. ***With Yannek I. Leiderman, MD, PhD***

Many of us may not have the luxury of consistently operating with trained fellows or surgical assistants. An important trend in modern-day vitreoretinal surgery has been minimizing dependence on an assistant.

In this regard, foot-pedal-controlled, non-contact, wide-angle viewing systems have been an important technology for independent surgery. Scleral indentation-assisted peripheral vitrectomy often still requires an assistant. However, in the absence of a skilled assistant, a chandelier enables a surgeon to indent with one hand and cut vitreous with the other. For routine cases, surgeons may hesitate to create an additional (fourth) sclerotomy for chandelier placement.

Here, Yannek Leiderman, MD, PhD, of Illinois Eye and Ear Infirmary shares a simple but valuable pearl for performing scleral indentation-assisted peripheral vitrectomy without an assistant.

Use Existing Cannulas

This technique involves inserting the chandelier in one of the two already placed open cannulas, reserving the other available cannula for the vitreous cutter held in one hand and freeing the other hand for the scleral depressor. Peripheral vitrectomy and vitreous base shaving do not require a second active instrument. Placing the chandelier in a pre-existing surgical cannula obviates the need for additional sclerotomies and may be performed immediately prior to peripheral vitrectomy.

Here, Dr. Leiderman shares some valuable tips for independent peripheral vitreous surgery.

Gooseneck-like Lamp

Place the chandelier via one of the instrument cannulas with the semi-rigid cable oriented like a gooseneck lamp (*Figure A*).

This facilitates optimal peripheral illumination and minimizes inadvertent misdirection of the chandelier. Often only a single reorientation of the chandelier to the contralateral hemi-fundus is necessary after the initial six clock-hours of peripheral maneuvers.

Use Nasal Instrument Cannula

The most efficient way to perform pseudophakic peripheral vitrectomy is to place the chandelier in the nasal instrument cannula. Peripheral vitrectomy may be performed circumscribing 360° via the temporal instrument cannula.

To minimize any constraints to movement of the vitrectomy probe,

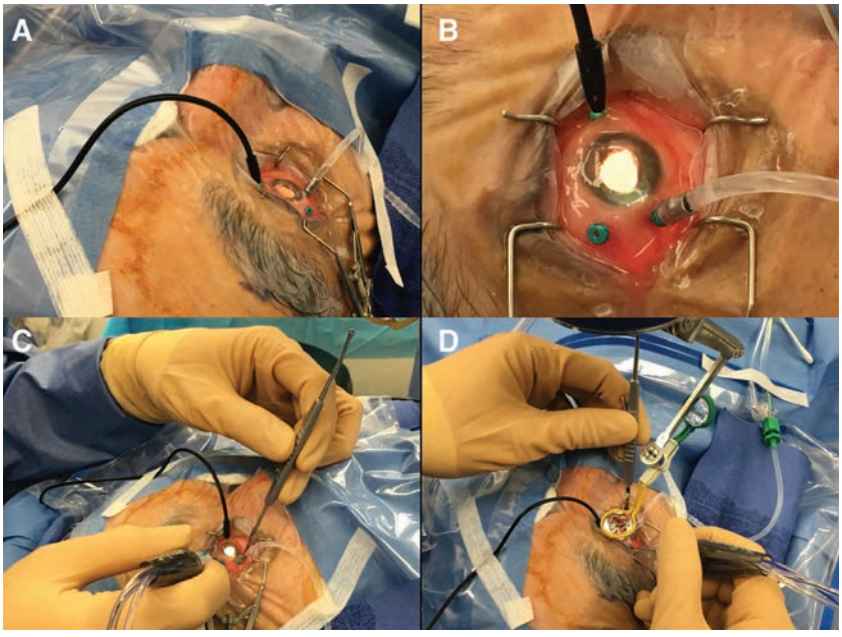

Figure. Placement of a chandelier endoilluminator via a pre-existing vitrectomy instrument cannula allows the surgeon to perform simultaneous peripheral vitreous surgical maneuvers and scleral indentation. Key steps are: A) orient the semi-rigid cable like a gooseneck lamp to allow for optimal peripheral illumination and minimize inadvertent misdirection of the chandelier; B) orient the cannulas for unconstrained maneuverability of the active instrument, which facilitates the next two steps: C) simultaneous peripheral vitrectomy; and D) scleral indentation by the surgeon.

View the Video

Yannek I. Leiderman, MD, PhD, demonstrates his technique for using chandelier endoillumination for peripheral vitreoretinal surgery when a surgical assistant is not available. Available at: http://bit.ly/RS_VideoPearl_005

place the port close to the temporal horizontal meridian. Simultaneous scleral indentation and peripheral maneuvers at the temporal horizontal meridian present the greatest challenge when the chandelier is placed in the nasal instrument port. This is most effectively addressed by inserting the scleral depressor into the temporal fornix from above or below the temporal cannula.

Alternate Cannulas

Phakic peripheral vitrectomy may require alternating the chandelier between the nasal and temporal cannulas to minimize passing the vitrectomy probe across the antero-posterior axis of the crystalline lens in removing contralateral peripheral vitreous.

Advantages of Chandelier

A chandelier endoilluminator allows the surgeon to simultaneously perform scleral indentation and use the vitrectomy probe, enabling dynamic and coordinated peripheral surgery that is more controlled and efficient, and may very well confer an improved margin of safety.

Dr. Leiderman's pearl to place the chandelier in one of the already placed cannulas eliminates the need for an additional sclerotomy for vitreous base shaving. True bimanual intraocular techniques will still require a fourth sclerotomy. I have routinely adopted this simple but efficient tip from Dr. Leiderman to perform vitreous surgery independently. RS

Dr. Hahn is an associate at New Jersey Retina in Teaneck. Dr. Leiderman is associate professor of ophthalmology in the retina service at Illinois Eye and Ear Infirmary, University of Illinois at Chicago.

Pipeline Update

(Continued from page 33)

in treatment-naive patients with wet AMD and a randomized, controlled trial to assess Zimura monotherapy in Stargardt disease. It has an open-label Phase IIa trial evaluating Zimura in combination with anti-VEGF therapy for idiopathic polypoidal choroidal vasculopathy. Ophthotech also said last year that in 2018 it would launch a Phase IIa trial of Zimura monotherapy for intermediate/posterior non-infectious uveitis.

Lampalizumab (Roche/Genentech). This is one agent for geographic atrophy that will not emerge from the pipeline soon. In reporting its 2017 results earlier this year, Roche disclosed that it was discontinuing Phase III trials of the lampalizumab program. The company also removed lampalizumab from its online Produce Development Portfolio.

Diabetic Macular Edema

Luminate (Allegro Ophthalmics). This year, Allegro Ophthalmics plans to initiate a Phase III trial of its lead integrin peptide therapy candidate, Luminate, for treatment of DME, president Vicken Karageozian, MD, said at the Ophthalmology Innovation Summit 2017. Luminate is a first-in-class drug that targets the integrin receptors involved in neovascularization by disrupting growth factor production

The Phase IIb DEL MAR trial showed that sequential therapy of Luminate with bevacizumab (Avastin, Roche/Genentech) was superior to bevacizumab monotherapy and Luminate/bevacizumab combination therapy, leading to a 7.1-letter gain in best corrected visual acuity at 20 weeks vs. 6.7 letters and 1.4 letters, respectively. Allegro anticipates making major funding decisions before commencing the Phase III trial.

RG7716 (Roche/Genentech). RG7716 in DME was the subject of encouraging results reported in February at the Angiogenesis meeting in Miami.[5] The BOULEVARD Phase II trial assessed two doses of RG7716 (1.5 mg and 6 mg) vs. monthly ranibizumab (0.3 mg). The study met its primary endpoint—improvement in adjusted best-corrected visual acuity at week 24: 13.9 chart-letter improvement in the 6-mg RG7716 group vs. 11.7 letters in the 1.5-mg RG7716 group and 10.3 letters in the 0.3-mg ranibizumab group.

AKB-9778 (Aerpio Therapeutics). This small-molecule agent is designed to target the Tie2/VE-PTP pathway in non-proliferative diabetic retinopathy. The drug is administered subcutaneously. AKB-9778 binds to and inhibits vascular endothelial phosphotyrosine phosphatase, a critical negative regulator of Tie2. AKB-9778 has demonstrated it activates the Tie2 receptor irrespective of extracellular levels of its binding ligands, Ang-1 (agonist) or Ang-2 (antagonist). The company is on schedule with its TIME Phase IIb clinical trial of AKB-9778, completing patient enrollment in February with a readout expected in the second quarter next year. RS

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

I Just Bought an OCTA. Now What?

There's already a CPT code for that. Here's why it suffices to submit claims for optical coherence tomography angiography.

Your latest purchase, a brand new optical coherence tomography angiography (OCTA) unit, just arrived at your office. The images are impressive. The details are like nothing you have seen from your current OCT. Your staff has been in-serviced on the equipment and now the administrator asks for guidance regarding the coding and billing of this new device. What do you say?

In this article, we discuss procedure coding for OCTA and explain why the current CPT code, 92134, suffices to report OCTA on a claim for reimbursement.

New Technology

Talisa de Carlo, MD, at New England Eye Center described OCTA as "a new, non-invasive imaging technique that generates volumetric angiography images in a matter of seconds."[1] Some OCTA devices use high-speed spectral domain or swept-source technology to capture images, while other OCTA devices use split-spectrum amplitude-decorrelation angiography to detect movement in blood vessels.[2]

Analyzing motion within the retinal or choroidal blood vessels with OCTA creates images of vessels and capillaries, but does not require injection of dyes or a contrast medium. Historically, ophthalmic angiography required injection of fluorescein or indocyanine green dye.

Computed tomographic angiography in other parts of the body is performed with and without contrast material, so extending this approach to vessels in the eye is a welcome advancement. Several companies, including Optovue, Heidelberg Engineering, and Zeiss Medical Technology, currently offer OCTA.

Terminology

In the context of OCTA, is the term "angiography" appropriate? *Taber's Medical Dictionary* defines angiography in two ways:[3]

1. A description of blood vessels and lymphatics.
2. Diagnostic or therapeutic radiography of the heart and blood vessels with a radiopaque contrast medium. Types include magnetic resonance angiography, interventional radiology and computed tomography.

Taber's also describes intravenous fluorescein angiography as:

Fluorescein dye is injected into an arm vein and sequential photographs are taken of the fundus as the dye circulates at different time intervals

Broadly speaking, the term "angiography" is appropriate because OCTA captures images and, through additional analysis, creates detailed images of the blood vessels within the retina and choroid. Conversely, the historic use of this term by ophthalmic technicians, medical assistants and billing staff assumes that dye is injected.

Coding for OCTA

Because OCTA provides additional information about the retina and macula beyond traditional OCT, the question retina specialists often ask is, "Can I use another CPT code in addition to 92134 to describe the added utility of this service?" The code they sometimes suggest is 92499—"unlisted ophthalmological procedure or service."

In the *2018 AMA CPT Professional Edition*, the first occurrence of the term "angiography" in the section devoted to ophthalmology is 92235—"Fluorescein angiography, with interpretation and report." Next is 92240—"Indocyanine green angiography, with interpretation and report."

However, neither code accurately describes OCTA; it uses neither fluorescein nor ICG dyes. CPT code 92134—"Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; retina"—describes OCT of the retina and associated structures (retinal layers, macula and retinal blood vessels).[4] The February *2011 CPT Assistant* discusses CPT 92134 as:

For the posterior segment, two distinct areas are imaged using the new technology, the optic nerve and the retina. The evaluation of the images differs. Consequently, codes 92133 and 92134 have been added to report scanning computerized ophthalmic diagnostic imaging of the optic nerve and retina, respectively ... Code 92134 describes scanning computerized ophthalmic diagnostic imaging of the retina.[5]

An example of current coverage guidance from Medicare Administrative Contractor National Government Services Local Coverage Determination defines scanning computerized ophthalmic diagnostic imaging (SCODI) (L34380) as:

- *... a non-invasive, non-contact imaging technique. SCODI produces high-resolution, cross-sectional*

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By Richard Mark Kirkner »

Retina AI Platform Moves Forward

Autonomous artificial intelligence system aims to widen primary-care screening of diabetic retinopathy.

The American Diabetes Association estimates about 30 million Americans had diabetes in 2015, and a third of them have signs of diabetic retinopathy.[1] Getting all them into ophthalmologists' or optometrists' offices for a diabetic retinal disease screening is impossible, let alone having certified readers review all those scans. That drove University of Iowa retina specialist Michael Abramoff, MD, PhD, to develop an artificial intelligence (AI) system that moves screening into the primary-care practice and utilizes an algorithm to evaluate the scans for signs of diabetic retinopathy.

Dr. Abramoff is founder and president of IDx, a private company developing an autonomous AI platform for evaluating retinal images for diabetic retinopathy. The company recently took a couple of steps toward commercializing its technology.

In February, the Iowa City-based venture submitted a *de novo* application to the Food and Drug Administration for the IDx-DR AI system. Two weeks later, Dr. Abramoff reported that a pivotal FDA trial of IDx-DR met its key endpoints for identifying DR in a diabetic population.[2]

Michael Abramoff, MD, PhD, delivers results of the IDx-DR pivotal trial at the Macula Society meeting in February.

Seed Planted In Residency

Dr. Abramoff, a professor at the University of Iowa Carver College of Medicine department of ophthalmology and visual science, also in Iowa City, tells *Innovation Insight* that the idea grew out of an observation he made as a resident evaluating retinas of patients with diabetes. "I realized what I was doing—looking at people who had nothing wrong with their retinas—maybe could be done more efficiently by a computer," he says. It took a couple of decades for AI to emerge and make that possible.

The concept behind IDx-DR is to make early detection of diabetic eye disease more accessible and affordable for patients by pushing highly reproducible technology into primary-care offices. The IDx-DR system requires assistants to operate a robotic camera that captures retinal images with a high degree of reliability and reproducibility.

Dr. Abramoff explains that if the AI algorithm determines any captured image is insufficient for analysis, the robotic camera instantaneously tells the operator, who can then capture new scans before the patient leaves the chair. The images are then sent to the AI database, which uses an algorithm to analyze them for signs of DR.

The AI algorithm incorporates deep-learning-based lesion detectors to identify DR, including diabetic macular edema. The trial evaluated IDx-DR by comparing it to standardized imaging and grading protocols by the Wisconsin Fundus Photograph Reading Center (FPRC). FPRC grading includes Early Treatment Diabetic Retinopathy Study Severity Scale (ETDRS) and DME determinations from widefield stereoscopic photographs and macular optical coherence tomography.

Pivotal Trial Findings

The FDA pivotal trial involved 10 different primary-care sites and prospectively enrolled 900 people with diabetes, 819 of whom could be fully evaluated by both AI and FRPC. The trial defined more-than-mild DR (mtmDR) as ETDRS level 35 or higher and DME in at least one eye. System operators in the primary-care practices had four hours of training while FPRC-certified photographers conducted the FPRC imaging.

Dr. Abramoff reported the results at the 41st annual Macula Society meeting in Beverly Hills, Calif.

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Moving the Needle on Ocular Cancer

How AU-011 selectively targets melanoma without damaging nearby ocular tissue.

By Richard Mark Kirkner

AU-011, Aura Biosciences' novel viral nanoparticle conjugate candidate, could be the first advance for treatment of ocular cancers since brachytherapy emerged decades ago. The Food and Drug Administration has granted AU-011 orphan drug and fast-track designations.

Conventional treatment for ocular melanoma involves radiotherapy, most commonly in the form of brachytherapy that requires surgical placement of a radioactive plaque on the sclera overlying the choroid. This technique requires multiple operations to place and remove the plaque, and can damage adjacent ocular structures.

AU-011 involves intravitreal injection of the tumor targeted drug, and then uses a laser to activate it. The platform is derived from technology that John Schiller, PhD, of the Center for Cancer Research at the National Cancer Institute had developed.

Preclinical results have demonstrated that AU-011 could selectively destroy ocular melanoma tumors in rabbit eyes.[1] At the American Academy of Ophthalmology Retina Subspecialty Day last year, Carol Shields, MD, of Wills Eye Hospital in Philadelphia, reported interim data from the Phase Ib/II trial that showed the drug was well-tolerated at three to six months in the first six patients treated.[2] Now, Aura is conducting a dose optimization study with plans to go into Phase III as early as next year.

Here, Aura founder and CEO Elisabet de los Pinos, PhD, and Chief Medical Officer Cadmus Rich, MD, answer questions about AU-011.

Q The mechanism of action in their own words

A Dr. de los Pinos explains AU-011 attaches to heparan sulfate proteoglycans (HSPGs) that are highly expressed and modified on the tumor cell membrane. The viral nanoparticle is just the protein shell that forms the capsid of a virus and it is conjugated to a light activatable cancer drug. It selectively targets and binds the melanoma cells in the eye.

Six hours after AU-011 is injected intravitreally, near infrared light is applied with an ophthalmic laser to activate the agent, a process that disrupts the tumor cell membrane. This leads to acute tumor cell necrosis.

The light-activated treatment is double specific: The drug spares surrounding, non-cancerous tissue because it is so specifically targeted to the tumor cells; and the laser light focuses only on the lesion, which ensures the activation of the drug exclusively in the area of the tumor.

Dr. Rich notes that AU-011 has no genetic material, so it will not multiply or spread when injected.

Q What is the significance of the preclinical data?

A Dr. de los Pinos says the goal is to have a highly effective treatment that preserves vision and avoids the comorbidities of radiotherapy. Preclinical studies have reported that AU-011 selectively destroyed choroidal melanoma tumors both *in vitro* and *in vivo* in a rabbit model.[1] While the limitations of the animal model are well known for demonstrating the efficacy of drugs in other types of cancer, the rabbit model closely replicates the human eye and has more relevance in ocular cancer research. In the rabbit model, the tumor grows in the same layer of the eye—the choroid—as in human pathology.

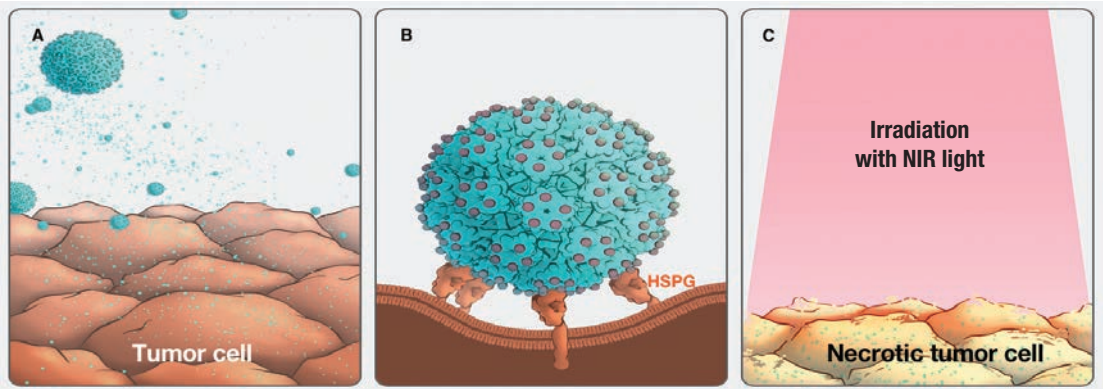
Highly regarded ocular pathologists from Massachusetts Eye and Ear Infirmary and Emory Eye Center replicated the data in multiple independent studies, Dr. de los Pinos says. Dr. Rich adds that the cells implanted in the rabbit eyes were human melanoma cells, and the preclinical results demonstrated that the drug was able to get to the choroid, bind to human melanoma cells and selectively kill the tumor cells while sparing the adjacent retina.

Q How does this compare to the current standard of care for ocular melanoma?

A Ocular melanoma is the most common primary tumor in the eye with a yearly incidence around 5-6 per million[3] and has a mortality rate of 50 percent at 10 years.[4] The traditional therapy had been enucleation of the affected eye, Dr. Rich explains.

That changed about 20 years ago when the Collaborative Ocular Melanoma Study (COMS) investigating radiation delivered via iodine^{125} brachytherapy for choroidal melanoma demonstrated a similar metastatic risk and mortality compared to enucleation.[5] The treatment evolved to also include external proton-beam radiation. Both forms of radiotherapy were relatively vision-sparing and eye-sparing compared to enucleation. However, the visual outcomes reported that a majority of patients had significant vision loss.

Since then, the standard of care of these primary tumors has not improved beyond radiotherapy. Different types of radio isotopes have been used, but up to 67 percent of patients will lose vision and 20 percent or more of these individuals will go legally blind in the eye after radiotherapy.[6] For large tumors or recurrent melanoma, enucleation is still an option.



Intravitreal injection (A) delivers viral nanoparticle conjugates (VNCs) to target tumor cells in the choroid. VNCs bind specifically to surface heparan sulfate proteoglycans on the tumor cell surface (B). Six hours after injection, ophthalmic laser (689 nm) activates the drug (C), disrupting the tumor cell membrane.

Q What are the risks of radiotherapy for treatment of ocular cancer?

A Radiotherapy delivers what Dr. Rich calls "poison" to the eye in the most direct, targeted methods possible—through brachytherapy or external beam therapy. The main problem is that radiation retinopathy, also known as radiation maculopathy, damages the fovea, or radiation papillopathy damages the optic nerve if the radiotherapy is too close to those structures. This can cause severe vision loss.

The operations to place and then remove the brachytherapy plaque, which has radioactive seeds to deliver radiation to the tumors, can require removal of extraocular muscles. That can cause diplopia postoperatively. Cataract and glaucoma are also potential sequelae.

External beam radiation is done through the front of the eye. Known side effects include decreased vision, similar to brachytherapy, along with dry eye, cataracts and neovascular glaucoma. Dr. Rich notes these are not benign treatments, but they do lead to local control of the choroidal melanoma.

Q How does targeted therapy advance treatment of ocular cancer?

A In cancer, the goal is to treat patients early in the disease course. Based on feedback Aura has received from ocular oncologists and retina specialists, AU-011 has the potential to give them a vision-preserving therapy that may be used earlier in the disease course than radiation, which because of its side effects, has typically been used when tumors have documented growth or are a certain size with risk factors. AU-011 has demonstrated a good safety profile that could enable the earlier treatment of smaller ocular tumors while preserving vision for patients, Dr. Rich says.

Q Where does the ongoing Phase Ib/II trial stand?

A Choroidal melanoma is a rare disease, so the trial is using a model with smaller dose-escalation cohorts, Dr. Rich says. The testing involves three ascending single dose treatments followed by light activation with a laser, and results so far show the agent is safe, well tolerated and does not affect vision.

Now the trial is moving into the multiple ascending dose-treatment phase, which is identifying the optimal regimen of AU-011 to maximize the efficacy of the drug while maintaining a good safety profile. Dr. Rich says the results are highly encouraging, but it's still very early in the trial.

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OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE

Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Diabetic Macular Edema

OZURDEX® is indicated for the treatment of diabetic macular edema.

CONTRAINDICATIONS

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

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product *[see Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection *[see Patient Counseling Information]*.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses *[see Adverse Reactions]*.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

ADVERSE REACTIONS

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

Adverse reactions associated with ophthalmic steroids including OZURDEX® include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Following a second injection of OZURDEX® (dexamethasone intravitreal implant) in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in the table below were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Ocular		
Cataract[1]	166/243[2] (68%)	49/230 (21%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

[2] 243 of the 324 OZURDEX® subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

	Treatment: N (%)	
IOP	**OZURDEX® N=324**	**Sham N=328**
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization,1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

Cataracts and Cataract Surgery

At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

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tomographic images of ocular structures and is used for the evaluation of anterior segment and posterior segment disease.

- *SCODI also permits high-resolution assessment of the retinal and choroidal layers, the presence of thickening associated with retinal edema, and of macular thickness measurement.*[6]

Considering these reliable sources, we conclude that 92134 should be used to report OCTA. The CPT description contains broad, inclusive language sufficient for this purpose. The omission of the term "angiography" from CPT 92134 does not mean the descriptor should be judged insufficient.

Because 92134 adequately describes OCTA, an additional CPT code is not necessary; it is duplicative. Use an unlisted code, such as 92499, only when a CPT code describing the service is not available.

And the Answer Is ...

To answer your administrator's original question regarding the coding and billing of OCTA, your answer is this: CPT 92134 applies. While your administrator may be disappointed, OCTA represents an advance in the current ophthalmic imaging technology. It provides additional information, saves time and lowers the patient's risk associated with intravenous injections of dye.

Within CPT, 92134 is broadly defined so it includes OCTA. The coverage indications listed in Medicare local coverage determination policies and by third-party payers for CPT 92134 apply to OCTA. Avoid adding CPT code 92499 to a claim for 92134, as it represents a billing error and may result in an overpayment.

No other CPT code is needed, and collecting additional payment from the patient is problematic for a host of reasons. With those words, enjoy your new technology, and code claims correctly. RS

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According to the presentation, the AI system detected mtmDR at a sensitivity of 87.2 percent and specificity of 90.7 percent. In 96 percent of subjects, it obtained high-quality images. Overall, 23.8 percent of participants had mtmDR.

Quotable

"With AI, you don't have the wait times. With AI, it takes minutes."

— Michael Abramoff, MD, PhD

Dr. Abramoff says AI-based systems have certain advantages over telemedicine, which he's also investigated. "With AI, you don't have the wait times. With AI, it takes minutes," he says. "The patients get the results immediately, and they get the referral immediately."

Another problem he points out with telemedicine is that the image quality is often insufficient, "but the patients have often left the primary-care office by the time a specialist reads it." He adds, "Telemedicine never had to do clinical trials."

The *de novo* FDA application means IDx-DR has no existing predicate in medicine. "There's no AI system that is autonomous like ours," Dr. Abramoff says. "There's no supervision by a physician. A lot of these AI systems involve assisting specialists; this is different."

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(continued from page 13)

going neovascular activity, but rather a residual anatomical space created by the failure of the neurosensory retina to reattach to the RPE as a consequence of nAMD.

One consequence of insisting upon a complete lack of IRF and SRF is more frequent injections, with the inherent ocular and potential systemic risks associated with them. Another possible ramification is accelerated geographic atrophy. The CATT trial two-year results revealed a 59-percent increase in the risk of geographic atrophy with two years of monthly injections (22.5 injections), regardless of the anti-VEGF drug used, compared with PRN treatment (13.1 injections).[15]

Furthermore, some evidence shows that SRF could have a protective effect against GA. A sub-group analysis of patients in the CATT trial found that patients with subfoveal SRF greater than 25 µm had a lower risk of GA development.[16] Conversely, eyes with IRF involving the foveal center or an area away from it had a higher risk of developing GA than eyes without IRF.

Bottom Line

There remains a need to tailor therapy for individual nAMD patients, and opportunities to further optimize treatment need to be explored and understood. The FLUID study, an ongoing, prospective multicenter trial, is investigating whether patients can tolerate a small amount of SRF with no adverse effect on visual outcome.[17] While established OCT biomarkers such as central retinal thickness, presence of subretinal scarring and inner segment/outer segment photoreceptor integrity remain important,[18] newer biomarkers such as the presence of SRF and IRF will help retina specialists choose long-term care for their nAMD patients.

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- Achieves clinically significant 3-line gains in BCVA[1,‡]
- Significantly reduces vitreous haze vs sham in noninfectious posterior segment uveitis[1]

*Diabetic macular edema. †Retinal vein occlusion: branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). ‡Best-corrected visual acuity.

Indications and Usage
Diabetic Macular Edema: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Retinal Vein Occlusion: OZURDEX® is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of noninfectious uveitis affecting the posterior segment of the eye.

Dosage and Administration: FOR OPHTHALMIC INTRAVITREAL INJECTION. The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

IMPORTANT SAFETY INFORMATION
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

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

Warnings and Precautions
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Adverse Reactions
Diabetic Macular Edema
Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® (dexamethasone intravitreal implant) for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® patients versus 4% of sham patients. 42% of the patients who received OZURDEX® were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

Retinal Vein Occlusion and Posterior Segment Uveitis
Adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

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

Reference: 1. OZURDEX® Prescribing Information.

Treat early with Ozurdex® (dexamethasone intravitreal implant) 0.7 mg

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