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RETINA SPECIALIST

JUNE 2017

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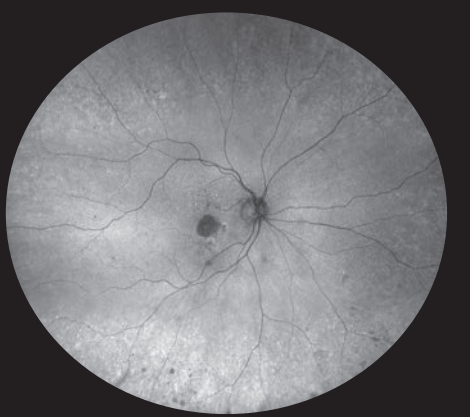

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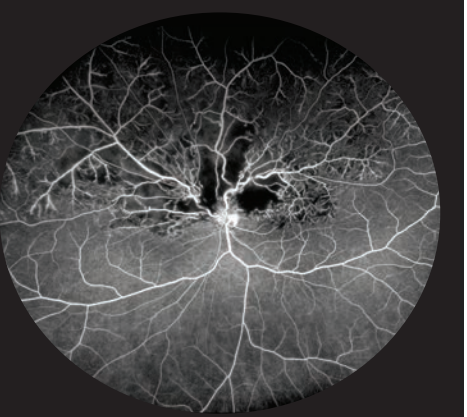

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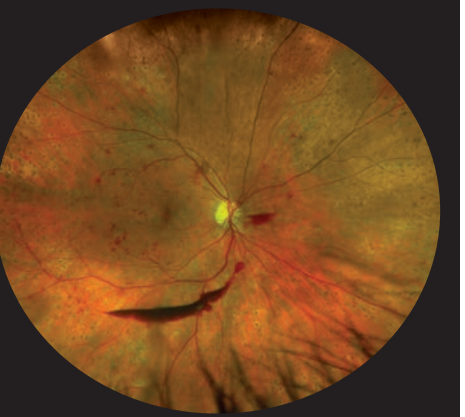

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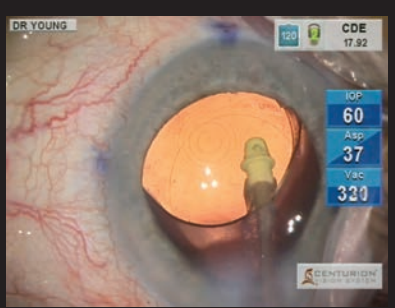
JUNE 2017

FEATURES

MANAGEMENT OF NONINFECTIOUS UVEITIS



DEPARTMENTS

NOW APPROVED

THE **FIRST** & **ONLY** ANTI-VEGF FOR PATIENTS WITH MYOPIC CHOROIDAL NEOVASCULARIZATION (mCNV)

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.[1-8]

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

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 adjacent 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 treatment–controlled study; key clinical outcomes at month 3.[1-8]

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.** Wolf S, et al; RADIANCE Study Group. *Ophthalmology.* 2014;121:682-692.

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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 (Non Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR)) in patients with Diabetic Macular Edema (DME)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

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

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.7, 2.8) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.8 in the full prescribing information)]*.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(2) 2017

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By Charles C. Wykoff, MD, PhD

Summer Reading

Growing up, I was not the reading type. I was the kid on the bike, the ball field or 20 feet up in the neighbor's valley oak. Unfortunately, it wasn't until high school that I realized the power of reading. Ayn Rand, who shares my birthday, published the first book that transformed the way I see the world: *The Fountainhead*.

The end of the school year is a great time to revisit what's on your reading list. In need of suggestions? Check out Bill Gate's blog, "gatesnotes." Some of his all-time favorites are *The Better Angels of Our Nature* by Steven Pinker and *Business Adventure* by John Brooks. The treasure I'm in the midst of currently has brought me deeper understanding of myself and one of my kids in particular, *Quiet: The Power of Introverts in a World That Can't Stop Talking* by Susan Cain. Want a quick, powerful novel? Grab *The Road* by Cormac McCarthy. If you have any favorites, I'd love to hear about them.

Reading makes me appreciate different perspectives, lets me see through another's eyes and expands my sphere of appreciation. It also forces me to define my own opinions and biases. While *Retina Specialist* is not intended to compete with a well penned book, I hope that some of the pieces in this and future editions will encourage you to think differently about your management of retinal diseases.

Do it the old fashion way. My kids read from a Kindle. I prefer paperbacks. There's fulfillment that comes from turning pages, taking notes in the margins and dog-earing good sections. I seldom come back to the notes or the dog-ears, but the act of recognizing quality sections makes the content stick better in my mind.

Sometimes I tell myself I'm too busy to read and weeks or months go by without picking up a book. When I do jump back in to the right book, it's refreshing. Like going back to 2,000 cuts per minute during a vitrectomy, when you jump back to 16,000 (or whatever your machine's fastest cut rate is), you find renewed appreciation for what was missing.

I find it ironic that Steve Jobs did all he could to keep his kids away from the iPad. In a world inundated with digital information and distractions, make time to unplug. Dive into a book this summer. Let me know what's on your summer reading list.

Quotable

"Reading makes me appreciate different perspectives, lets me see through another's eyes and expands my sphere of appreciation. It also forces me to define my own opinions and biases."

IN BRIEF

• The Food and Drug Administration approved **Lucentis** (**Genentech**, ranibizumab) 0.3 mg for monthly treatment of all forms of diabetic retinopathy. Lucentis is now approved to treat diabetic retinopathy either with or without diabetic macular edema.

• **Genentech** also received FDA approval for **Actemra** (tocilizumab) subcutaneous injection for the treatment of giant cell arteritis (GCA). Actemra is the first FDA-approved treatment for adult patients with GCA.

• **Bausch + Lomb** received 510(k) FDA clearance for its **Vitesse** hypersonic, 100 percent open-port vitrectomy system. The technology will be featured exclusively on the new Stellaris Elite Vision Enhancement System.

• A Phase I dose-escalation study of **X-82** (vorolanib), an oral tyrosine kinase inhibitor for neovascular age-related macular degeneration and the lead candidate of biopharmaceutical company **Tyrogenex**, met its primary endpoint of no serious adverse events. Also, 60 percent of the 25 patients who completed 24 weeks of treatment required no anti-VEGF injections. The results were published in the June 1 issue of *JAMA Ophthalmology*.

Study Evaluates Risks For Steroid-Induced IOP Rise in Uveitis

Ocular hypertension is a confounding sequela of corticosteroid therapy in adults with noninfectious uveitis, but a retrospective multicenter study of more than 5,000 eyes provides insight into adults most vulnerable to intraocular pressure spikes while on systemic corticosteroid therapy for the condition.[1]

The study involved 3,306 patients with noninfectious uveitis and 5,270 uveitic eyes seen at five uveitis clinics in the United States between 1979 and 2007. The main outcome was prevalent and incident ocular hypertension (OHT) with intraocular pressures (IOPs) of ≥21 mmHg, ≥30 mmHg and increase of ≥10 mmHg from baseline or need for treatment.

Among the study eyes, the average annual incidence rates were 14.4 percent for OHT of ≥21 mmHg (95% confidence interval [CI], 13.4–15.5) and 5.1 percent for OHT of ≥30 mmHg (95 percent CI, 4.7–5.6).

The study identified the following statistically significant risk factors (and adjusted hazard ratios [aHR]) for incident OHT ≥30 mmHg:

- Systemic hypertension (1.29).
- Presenting visual acuity of ≤20/200 vs. ≥20/40 (1.47).
- Pars plana vitrectomy (1.87).
- History of OHT in the other eye: IOP ≥21 mmHg (2.68); ≥30 mmHg (4.86); and prior/current use of IOP-lowering drops or surgery in the other eye (4.17).
- Anterior chamber cells 1+ (1.43) and ≥2+ (1.59) vs. none.
- Epiretinal membrane (1.25).
- Peripheral anterior synechiae (1.81).
- Current prednisone use >7.5 mg/day (1.86).
- Periocular corticosteroids in the last three months (2.23).
- Current topical corticosteroid use of more than eight times a day vs. none (2.58).
- History of fluocinolone acetonide implants (9.75).

The study authors also identified two predictors of statistically lower risk of OHT: a history of bilateral uveitis (aHR, 0.69); and a history of hypotony (aHR, 0.43).

"Patients with one or more of the several risk factors identified are at particularly high risk and must be carefully managed," concluded lead author Ebenezer Daniel, MBBS, PhD, of Scheie Eye Institute, Philadelphia, and colleagues.

"Modifiable risk factors, such as use of corticosteroids, suggest opportunities to reduce OHT risk within the constraints of the overriding need to control the primary ocular inflammatory disease," Dr. Daniel and colleagues stated.

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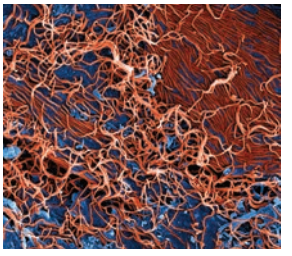
Previously Unseen Retinal Lesions Reported in Ebola Survivors

As reports of new Ebola cases trickle out of western Africa, investigators have identified previously unseen retinal lesions in survivors of previous outbreaks, according to a study published in the journal *Emerging Infectious Disease*.[1]

Paul J. Steptoe, of the University of Liverpool and Royal Liverpool Hospital, and colleagues from the U.K. and Sierra Leone conducted a prospective, case-control study in that country to determine if Ebola virus disease (EVD) had any specific effects on the back of the eye. They subclassified retinal lesions into 10 different groups, and noted type 6 subcategory lesions appeared exclusively in the EVD survivors. The presentation was bilateral in half of them.



Colorized scanning electron micrograph of filamentous Ebola virus particles (red) attached and budding from a chronically infected VERO E6 cell (blue) (25,000-x magnification). *National Institute of Allergy and Infectious Diseases, National Institutes of Health photo*

The study involved 82 EVD survivors and 105 controls that had ophthalmic examinations. The researchers reported that 14.6 percent of EVD survivors (97.5 percent confidence interval [CI], 7.1–25.6) had the novel retinal lesion along optic nerve axons. They observed any retinal lesions other than type 6 in 21 of 82 patients (25.6 percent, 97.5 percent CI, 15.5–38) of EVD survivors and 25 of 105 (23.8 percent, 97.5 percent CI, 15.1–34.4) of controls. The high rate of retinal lesions in controls may be attributed to the prevalence of uveitis in Sierra Leone, where it is the second leading cause of blindness after cataracts.

The distribution of the retinal lesions in EVD survivors suggests a spread from the optic nerve and along retinal ganglion cell axons. In the eight cases in which lesions appeared adjacent to the optic disc, their curvilinear projections from the disc margin appeared to align with the anatomic pathways of the retinal ganglion cell axons that constitute the optic nerve. The other possible mode of entry into the eye is hematologic, but the study found no signs of associated vascular involvement.

With regard to appearance of the lesions, the study authors described characteristic angulated borders like a diamond or wedge not found in any other retinal lesion. And despite the close proximity of the lesions to the optic nerve, the study noted no optic nerve inflammation or pallor, and the EVD retinal lesions did not affect visual acuity. Cataract was the most common cause of visual impairment in EVD survivors. This study suggests testing the anterior chamber for Ebola before proceeding with cataract surgery in EVD survivors.

The Democratic Republic of Congo reported an outbreak of four Ebola cases and four deaths in May, but no new confirmed cases since. In Sierra Leone, almost 4,000 people died and about 10,000 survived previous Ebola outbreaks. RS

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Pharmacogenetics and AMD: Is AREDS Helpful? An Industry CEO Weighs In

Editor: I read with interest the article, "Pharmacogenetics and AMD: What we Know (and Don't Know) So Far" by Parth Shah and Stephen G. Schwartz, MD, MBA (*Retina Specialist, page 26, March 2017*). They reviewed genetic tests for age-related macular degeneration for their prognostic value and for potential pharmacogenetic interaction with the Age-Related Eye Disease Study (AREDS).

They reviewed numerous reports related to the safety and efficacy of AREDS in the treatment of patients with intermediate AMD. Contrary to the authors' note, Michael Klein, MD, and coauthors did not find that patients with two high-risk complement factor H (CFH) alleles had a statistically significant benefit from AREDS.

The authors pointed to the AREDS 38 publication, suggesting that all evaluated patients benefited from AREDS.[1] However, for patients with the C2A0 genetic profile the hazard ratio (HR) for progression on AREDS vs. placebo was 1.78. These patients did not benefit from AREDS and they trended toward harm.

The authors also referenced a letter to the editor by Emily Chew, MD, detailing a report on 526 patients.[2] There is no statistical analysis in this letter demonstrating the authors' conclusions or that AREDS was beneficial to anyone. A proper scientific discussion on these data is long overdue.

The authors said that Johanna Seddon, MD, MSc, and colleagues reported that "antioxidants and zinc conferred no treatment benefits in patients with two risk alleles at CFH or no risk alleles at ARMS2" (C2A0 genotype).[3] Dr. Seddon and colleagues did not analyze the C2A0 genotype alone; they combined it with the C1A0 genotype and showed that 33 percent of patients do not benefit and, in fact, trend toward harm from choroidal neovascularization (CNV) (HR=1.54). They said more study was needed to understand the biology behind this interaction, not to see if an interaction exists.

Is AREDS helpful or possibly harmful? All of the published studies, including AREDS 38, show that patients with the C2A0 genotype (13 to 19 percent of patients) either do not benefit or they may be harmed.

The authors suggested prognostic genetic testing confers no benefit because it is no better than the clinical eye examination. Many authors have demonstrated a statistically significant increased accuracy of adding genetics to the clinical eye exam with phenotype groups. In the model Dr. Seddon and colleagues developed, a typical five-year range of risk for patients with AREDS category 3 AMD would be 7 to 70 percent.[4] According to the American Academy of Ophthalmology Preferred Practice Patterns, one would not manage these AREDS category 3 patients with higher or lower risk the same way.

Some prognostic studies that did not show statistical significance when genetics were added to the clinical eye examination included large groups of patients with AREDS category 1 disease.[5] The eye examination is just as accurate in these cases because they do not progress in five to 10 years.

The MARINA study showed that patients with CNV referred early, when their visual acuity was 20/80 or better, had better outcomes from anti-VEGF treatment.[6] Because the primary eye-care professional plays a key role in early treatment, the accuracy of AMD risk assessment is important.

Personalized medicine is a valuable tool in AMD. While the subject is controversial, the data are not. All the published data and the recent Centers for Medicare and Medicaid Services approval for reimbursement of pharmacogenetic testing show that AMD is predominately a genetic disease, and that personalized medicine is a useful prognostic and pharmacogenetic tool.

— Gregory Hines
president and CEO
Arctic Medical Laboratories
Grand Rapids, Mich.

Editor's note: *The authors chose not to respond to Mr. Hines' letter.*

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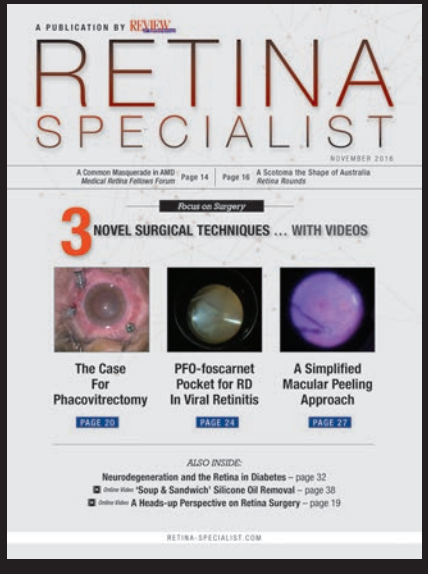

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By Elie Motulsky, MD, PhD, and
Philip J. Rosenfeld, MD, PhD

Double-Layer Sign and Type 1 CNV

How OCT can be a powerful tool for detecting choroidal neovascularization in a variety of retinal diseases.

Optical coherence tomography is a fast, non-invasive and reproducible imaging modality useful for diagnosing and managing patients with exudative retinal diseases.[1,2]

In age-related macular degeneration (AMD), central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy (PCV), high myopia and uveitic diseases, choroidal neovascularization (CNV) can be a vision-threatening complication.[3-5] The most common type of neovascularization that develops in these conditions is type 1 CNV, which arises from the choriocapillaris, penetrates through Bruch's membrane (BM) and resides between the retinal pigment epithelium (RPE) and BM.

While patients and clinicians become aware of type 1 CNV once intraretinal, subretinal or sub-RPE fluid accumulates within the macula, the presence of a low-lying fibrovascular retinal pigment epithelial detachment (PED) often goes unnoticed and can be a harbinger of visual distortion due to fluid accumulation. A highly underappreciated anatomic feature on optical coherence tomography (OCT) B-scans that indicates early stage type 1 CNV is a low-lying PED referred to as the "double-layer sign" or DLS.[6]

What Is 'Double-layer Sign'?

The presence of a DLS, which suggests the possibility of type 1 CNV, was initially reported in PCV.[6] The DLS is an OCT feature consisting of a two reflective bands, one on top of the other with a small space in between. The upper band corresponds to the RPE, the lower band to BM and the space in between to the CNV. Regardless of the underlying retinal disease, the DLS represents the space generated by the type 1 CNV, which resides between the RPE and BM.

How OCT-A Can Help

While a DLS suggests the presence of CNV, OCT angiography (OCT-A) can determine its actual presence. OCT-A detects blood flow by acquiring multiple B-scans at the same position and then applying a decorrelation algorithm to the datasets to detect flow. This method can differentiate moving particles from within blood vessels from the surrounding static tissue.

Algorithms can then generate en face structure and flow images. These en face flow images can be color-coded to represent different vascular layers in the retina and choroid. The en face image can be refined further by selecting particular slabs that represent distinct boundary layers. By picking a segmentation strategy in which the boundary layers represent the RPE and BM, we are able to identify specific flow within this slab or within the DLS.[7] In the absence of fluid accumulation, OCT-A will help identify subclinical CNV.

Clinical Cases

Figures 1 and 2 offer clinical examples of OCT B-scans showing a DLS that represents type 1 CNV. In both figures, the top row shows examples of non-exudative neovascular AMD with type 1 CNV. The OCT B-scan with a DLS (*Figure 1A*) and the magnified area within the box (*Figure 1B*).

In the same case, the en face flow image (*Figure 2A*) shows a vascularized lesion under the RPE and the *en face* structure image (*Figure 2B*) shows an area of decreased intensity, which arises due to a space with decreased reflectivity compared with the surrounding tissue. These en face images correspond to a custom RPEFit segmentation strategy in which the inner boundary layer of the slab is the RPE and the outer boundary layer is BM. A horizontal

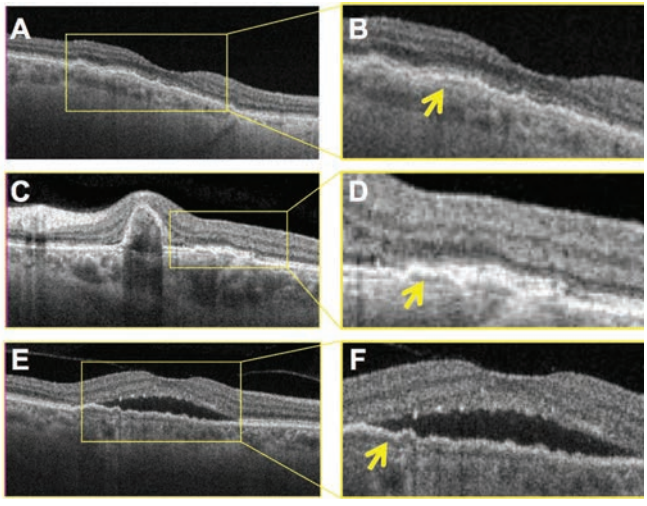

FIGURE 1. Swept-source optical coherence tomography (OCT) B-Scans show the "double-layer sign" (DLS) in three different disease processes with type 1 macular neovascularization: non-exudative age-related macular degeneration (A, B); polypoidal choroidal vasculopathy (C, D); and central serous choiroretinopathy (E, F). Magnified images (B, D, F) show DLS where the neovascularization resides between Bruch's membrane and the retinal pigment epithelium (arrows).

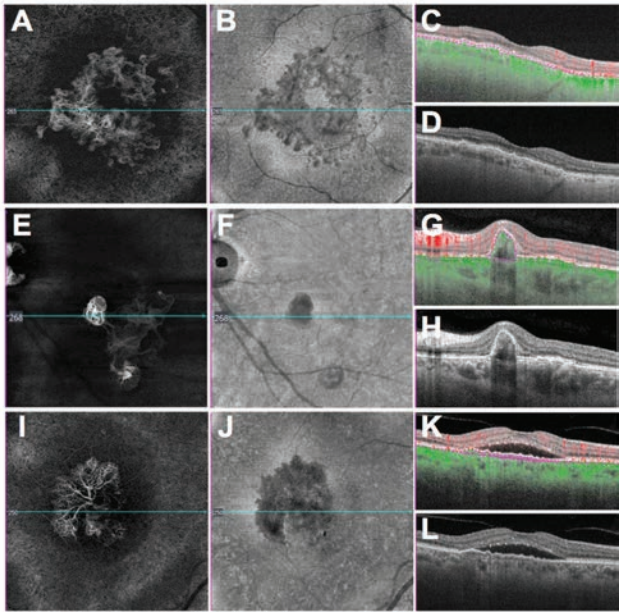

FIGURE 2. Swept-source optical coherence angiographic images show the neovascular lesions that correspond to images in Figure 1: non-exudative age-related macular degeneration (A,B,C,D); polypoidal choroidal vasculopathy (E, F, G, H); central serous choiroretinopathy (I, J, K, L); en face flow images using a slab with boundaries between the retinal pigment epithelium (RPE) and Bruch's membrane (A, E, I) and corresponding en face structure images from the same slab (B, F, J); B-scans with and without superimposed color-coded flow with red representing flow above the RPE and green representing flow beneath the RPE (C, D, G, H, K, L); and B-scan images with purple dashed boundaries corresponding to the en face images (C, G, K).

foveal B-scan depicts the boundary layers as purple dashed lines and flow represented as red above the RPE and green below the RPE (*Figures 2C, D*).

The second row in both figures corresponds to an eye with PCV. The B-scan (*Figure 1C*) shows a peaked PED with an adjacent DLS corresponding to a branched vascularized network (BVN).

Magnified OCT B-scan better visualizes the DLS and the corresponding BVN (*Figure 1D*) while OCT-A en face flow imaging (*Figure 2E*) highlights the boundaries between the RPE and Bruch's membrane along with the adjacent polyps. As with the first case, the B-scans with and without flow and with the segmentation boundaries are shown (*Figures 2G, H*).

The last row of both figures corresponds to an eye with CSC that has type 1 CNV. As with the previous examples, the DLS is evident on the magnified frame from the B-scan (*Figure 1F*) and the typical appearance of type 1 CNV can be appreciated on the en face flow image (*Figure 2I*). Once again, structural en face imaging depicts an area of decreased signal intensity on the structural image (*Figure 2J*), which suggests that the flow signal is real and supports the diagnosis of CNV. While type 1 CNV always causes an elevation of the RPE, not all elevations of the RPE correspond to type 1 CNV.

We have the diagnostic tools to distinguish between vascularized and non-vascularized PEDs. Where a DLS can increase the suspicion of type 1 CNV, OCT-A can confirm it.

In our experience, swept-source OCT-A (SS-OCTA) does a better job of unambiguously identifying subtle non-exudative CNV than spectral-domain OCT-A. SS-OCTA may be even better than indocyanine green angiography. However, until SS-OCTA is widely available, routine structural OCT B-scans will provide the first clue as to whether type 1 CNV lurks beneath the RPE in eyes without exudation.

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***Disclosure:** Dr. Rosenfeld receives research support from and is a consultant for Carl Zeiss Meditec.*

Why Lesions and After-Image?

Concern for retinal tears in the fellow eye leads to a workup that goes in a different direction.

By Christine Petersen, MD, and Thellea K. Leveque, MD, MPH

A 59-year-old male came to the University of Washington Eye Institute complaining of blurry vision and floaters in the left eye for three days. Although he did not report any photopsias, he described a light after-image that persisted for less than one minute after he closed the left eye. He denied any vision changes in the right eye.

Medical History

His ocular history included radial keratotomy (RK) and cataract surgery in both eyes, and posterior vitreous detachment with multiple associated retinal tears in the right eye, which was treated with laser retinopexy about a year earlier. His medical history was unremarkable. Medications included ibuprofen, omeprazole and sildenafil. He denied any recent illness. Review of systems was negative.

Examination

Visual acuity was 20/15 in the right eye and 20/100 in the left, improving to 20/40 on pinhole. Intraocular pressures were 16 and 18 mmHg in the right and left eyes, respectively. No afferent pupillary defect was detected. Visual fields were full to confrontation in each eye.

Anterior segment exam showed bilateral corneal RK scars and posterior chamber intraocular lenses in good position, but was otherwise unremarkable. Dilated funduscopy showed a Weiss ring in both eyes, with pigmented laser surrounding retinal breaks in the right eye. The left eye had granular mottling of the foveal retinal pigment epithelium (RPE) and scattered deep yellow-white retinal lesions in the posterior pole and mid-periphery (*Figure 1A*) with mild to moderate retinal venous tortuosity compared to the fellow eye, but this was stable compared to previous fundus photos. We found no untreated retinal breaks on 360° scleral depression.

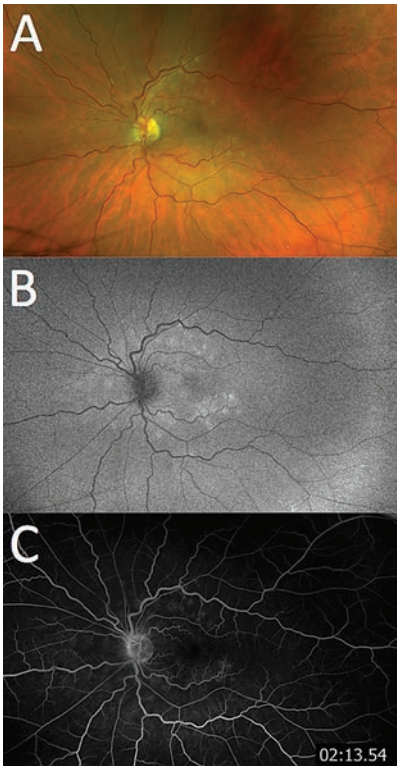

Figure 1. Color fundus photography (A) demonstrates multiple deep yellow-white lesions of the left eye, which correspond to hyperautofluorescence on fundus autofluorescence (B) and hyperfluorescent wreath-like lesions on fluorescein angiogram (C).

Diagnosis, Workup

Fundus autofluorescence (FAF) of the right eye was normal. The left eye had hyperautofluorescent areas corresponding to the yellow-white dots on color photos and clinical exam (*Figure 1B*). Fluorescein angiogram (FA) showed late hyperfluorescence of these lesions as well as mild leakage at the disc (*Figure 1C*). Optical coherence tomography (OCT) of the right eye was unremarkable but showed diffuse irregularity and patchy loss of the ellipsoid zone in the left eye (*Figure 2*).

Based on the patient's complaints and history of multiple retinal breaks in the right eye, we initially had high suspicion for a similar process in the left. However, exam findings and subsequent imaging led to a differential diagnosis that included infectious and noninfectious choroiditis. Complete blood count with differential, comprehensive metabolic panel and syphilis serologies were unremarkable.

Treatment

Given the classic findings on the fundus exam, OCT, FAF and FA, we diagnosed multiple evanescent white dot syndrome (MEWDS), a self-limiting disease. We counseled the patient on the natural history of MEWDS—typically spontaneous recovery over weeks to months with occasional persistent scotomas, dyschromatopsia or photopsias. This patient returned four weeks after the initial presentation. His vision improved to 20/30 and foveal granularity improved markedly both clinically and by OCT.

Discussion

While the patient's complaints and history of retinal tears in the fellow eye were concerning for a new retinal tear in the left eye, a careful exam and judicious workup led to the diagnosis

of MEWDS. First described in 1984, MEWDS is one of the several inflammatory chorioretinopathies known as white dot syndromes. These disorders have an unknown etiology but tend to affect young, healthy patients who present with photopsias, blurry vision, floaters, dyschromatopsia or scotomas. Funduscopic exam reveals characteristic yellow to white lesions that can affect the retina, RPE, choriocapillaris or choroid.[1]

MEWDS mostly affects young, healthy women and often appears in patients with moderate myopia. Although usually unilateral, authors have reported bilateral or recurrent disease. Funduscopic exam reveals multiple deep, white-to-yellow dots in the posterior pole of 100 to 200 µm or more in diameter. The number of dots can vary and they may be absent altogether. When present, the white dots tend to resolve within seven to 10 weeks. A pathognomonic yellow-orange granularity of the fovea may persist after resolution of other findings and symptoms. Other findings may include vitreous cell, optic disc edema and an afferent pupillary defect.[1–3]

Role of Ancillary Imaging

Ancillary imaging may aid in the diagnosis of MEWDS. Authors have reported that chorioretinal lesions are more numerous and easier to identify on FA, FAF and indocyanine green angiography (ICGA) than on clinical exam or color fundus photos.[2,4] FAF demonstrates increased autofluorescence of the lesions with surrounding hypoautofluorescence. Early phase FA reveals punctate hyperfluorescence in a wreath-like pattern, while later stages may show multifocal areas of mild staining. ICGA shows hypocyanescent lesions in later phases and usually more lesions than FA.[2–4]

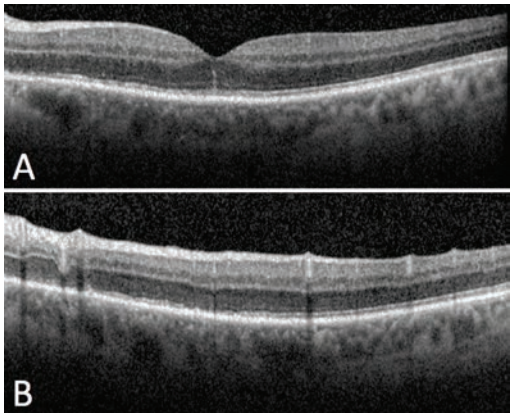

Figure 2. Spectral-domain optical coherence tomography (SD-OCT) of the left eye through the fovea (A) shows irregularity of the ellipsoid zone and a linear hyperfluorescent line extending into the outer nuclear layer. Through the superior macula (B), SD-OCT demonstrates irregularity and focal disruption of the ellipsoid zone.

Spectral-domain OCT through the fovea reveals irregularity or even disruption of the ellipsoid zone, which may also appear elsewhere in areas corresponding to other known lesions. As in this patient's case, hyper-reflective lines or spots may also extend to the outer nuclear layer[2,4].

Lesions seen on FA and ICGA have been classified as either "dots" or "spots." Dots are smaller (approximately 100 µm) and show the classic wreath-like configuration of hyperfluorescence on early phase FA. Spots are larger (<200 µm), stain late on FA, and are hypofluorescent on ICGA and hyperautofluorescent on FAF.

Francesco Pichi, MD, and colleagues demonstrated that when evaluated with *en-face* OCT, the dots and spots localize to the outer nuclear layer and the ellipsoid zone, respectively.[4] This may help elucidate the pathophysiology of MEWDS, which they propose is an inflammation of the photoreceptors leading to loss of the inner and outer segments of photoreceptors. They supported this by the fact that they did not see any abnormality of the choriocapillaris on *en-face* OCT. Marcela Marsiglia, MD, and colleagues also found no evidence of a primary disorder of the choroid, choriocapillaris or RPE in their multimodal imaging study and concluded that MEWDS is a reversible disease of the photoreceptors.[2]

MEWDS, because of its self-limiting nature, usually does not require treatment. Rarely, patients may develop choroidal neovascular membranes, which anti-VEGF injections may treat effectively.[1]

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By Paul Hahn, MD, PhD »

Air and Oil: Friend and Foe

Pearls for using or removing an air bubble to ensure a perfect silicone oil fill.

Silicone oil is an important tool in every vitreoretinal surgeon's toolbox, although we often shy away from using it because of its cost and potential complications. In the last issue, we presented a pearl for elegant placement of iris retention sutures to prevent anterior oil migration in complex cases involving a unicameral eye with iris loss. I received great feedback about this tip, but I also received requests for more basic tips for filling an eye with oil. Here, I present a set of pearls to help guarantee a perfect oil fill.

Non-aphakic Patients

In most non-aphakic patients, oil overfill is rare, as it immediately results in markedly elevated eye pressure and is easily detected by simple palpation of a rock-solid eye. Oil underfill is more common. I believe underfill is almost always caused by an air bubble sequestered within the vitreous cavity, usually hidden in the peripheral retrolenticular space and unable to exit through small-gauge cannulas that oil easily plugs.

Underfill results as the air is quickly absorbed and fluid replaces it. To avoid this, I recommend always inserting the light pipe back in the eye following completion of silicone oil filling to look for sequestered peripheral air bubbles. Aspirating these bubbles with an extrusion cannula (it helps to pull out the silicone tip) or the vitreous cutter followed by additional oil placement as needed to achieve a normal pressure will guarantee a perfect oil fill.

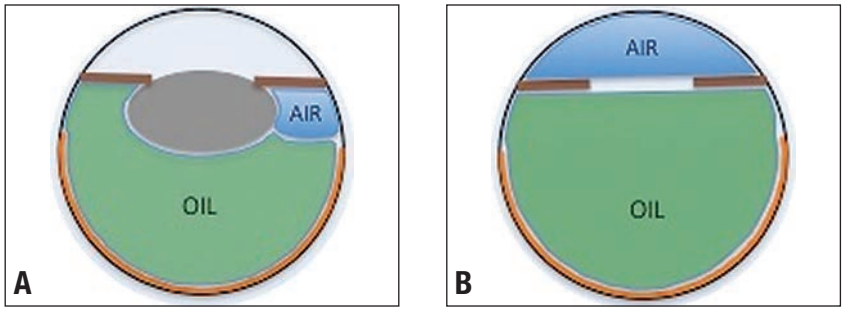


Figure. Air sequestered within the eye will lead to an underfill of silicone oil. A wide-angle viewing system can visualize sequestered air (A), which should be removed. In aphakic patients (B), filling the anterior chamber with air allows easy estimation of the posterior chamber volume for silicone oil filling. These tips apply for an air-oil exchange. Apply alternative techniques when performing a direct fluid-oil exchange.

Aphakic Patients

For aphakic patients, oil fill can be more complicated. Caution is needed to prevent both overfill (oil migrating into the anterior chamber) and underfill. I recommend adding an air bubble to fill both the anterior and posterior chambers. I then fill the posterior chamber with oil until I see the oil-air interface just posterior to the iris plane and top off to a normal pressure by palpation.

As above, I then insert a light pipe to remove any posteriorly sequestered air. By the first postoperative day, the air in the anterior chamber will be replaced by fluid, and the fill should be perfect. Of course, an inferior iridectomy is important.

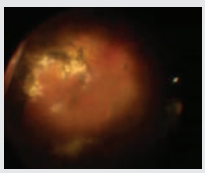
If oil is inadvertently overfilled, the oil-air interface will migrate into the anterior chamber and overfill is easy to identify. Extruding this excess oil and simultaneously infusing air, which will rise through the oil to refill the anterior chamber, will similarly ensure a perfect fill. With an air-filled anterior chamber in aphakic individuals, overfill is also rare unless an incision in the anterior chamber allows air to escape. This is because the oil does not rise above the air, and overfill would lead to an immediately firm eye.

These techniques work well in my hands and require no additional instrumentation or cost. Others have reported similar approaches using an extrusion cannula to completely remove air under direct visualization during oil infusion or viscoelastics to fill the anterior chamber.

Regardless of the technique, understanding the mechanisms of silicone oil underfill and overfill is critical to ensuring the optimal fill every time using the technique that works best for you.

Dr. Hahn is an associate at NJRetina in Teaneck, N.J.

View the Video



Watch as Dr. Hahn explains how to achieve a perfect silicone oil fill every time. Available at: http://bit.ly/RS_VideoPearl_002.

Series: Beyond the Retina

CATARACT SURGERY UPDATE FOR RETINA SURGEONS

Catching up with the rapid evolution of technology and techniques used in today's cataract surgery.

By Timothy N. Young, MD, PhD

As a cataract and anterior segment surgeon, I have always felt very fortunate to have ready access to the great abilities and expertise of my retinal specialist colleagues. I truly do sleep better at night knowing that you are there for my patients when they need it—which I hope is not that often, especially regarding cataract surgical complications.

In reality, with the ever-increasing wave of aging and elderly patients in our nation, we have a burgeoning need to continue to work effectively together to manage our patients' ophthalmic care. As our individual subspecialties advance at a fast pace, keeping up with important developments in other areas can be a daunting task. My goal here is to provide some brief but by no means exhaustive discussion of developments in cataract surgery.

IOL technology

As a cataract surgeon, I am glad to be practicing in an era in which we have many options for treating our patients with the best possible intraocular lens technology, and these options continue to expand. Indeed, it can be difficult to sift through and discuss all the possibilities to arrive at best treatments for individual patients.

- ***Torics.*** The availability of toric IOLs potentially applies to millions of patients who have clinically significant astigmatism and require cataract removal. Toric IOL offerings allow the accurate correction of corneal astigmatism up to 4 to 4.5 D or even more when combined with bioptic approaches such as corneal relaxing incisions or subsequent LASIK. Clearly, the dramatic reduction in glasses dependence can be life altering for these patients.

  It is gratifying for both surgeon and patient when a symptomatic cataract is cleared and the patient also has a newfound independence from glasses. Currently available toric IOLs show excellent long-term rotational stability when placed into the intact capsular bag.

  Other than out-of-pocket expense for a "premium" IOL upgrade, few downsides argue against the use of toric implants, which unlike multifocal

Take-home Point

Retina specialists and cataract surgeons frequently share complicated patients that require a high level of back-and-forth communication. This article reviews recent innovations in intraocular lens (IOL) and perioperative technology and cataract surgery techniques, ranging from toric and multifocal and extended depth-of-focus IOLs to intraoperative aberrometry to intracameral and intravitreal prophylaxis, so the retina specialist can be conversant with the cataract surgeon when managing these patients.

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DISCLOSURES: Dr. Young has no financial relationships to disclose.

IOLs, are not associated with unwanted optical side effects or reduced contrast sensitivity. For this reason, toric IOLs can be used even in patients with significant comorbidities, like the many patients we share with our retinal colleagues. However, patients with severe limitations of visual potential following cataract removal may not find additional glasses independence worth the out-of-pocket cost.

• ***Multifocal and extended depth-of-focus IOLs.*** Very likely as a retinal specialist, you have found yourself peering through a condensing lens at a macula that was a little blurred by the multifocal IOL "in the way." Maybe you have even thought something unkind about the cataract surgeon who put it there! Believe me, even though I am that guy on occasion, I think I speak for my colleagues when I say, "We feel your pain."

The multifocal IOL can be an unfortunate circumstance when it finds its way into an eye with significant macular pathology or when a healthy macula subsequently develops pathology, as the small loss of contrast sensitivity and optical aberrations associated with multifocals may compound the vision loss due to the macular disease.

However, the multifocal IOL does play an important role in satisfying the vision needs of the cataract patient who desires spectacle independence. As cataract surgeons, we must use multifocal IOLs wisely—that is, in well-chosen candidates who are free of macular and ocular surface disease. Fortunately, we are seeing some continued evolution of the IOL technology that shows promise for improved vision results, greater flexibility for meeting the vision goals of our patients and reduced visual side effects.

One recent addition to our portfolio of presbyopic IOLs is the extended depth of focus (EDOF) implant (Symfony, Abbott). This class of IOL resembles the multifocal IOL with a diffractive ring grating on the face; however, the optics produce an elongated focal zone rather than separate split focal points. This allows a useful range of near-vision function with less reduction of contrast sensitivity. Near vision is most robust in the intermediate range and some modest targeting of nondominant monovision may be needed for reading independence. The Symfony IOL also is available in four toric models that enable correction of up to 3 D of corneal astigmatism, which makes the lens applicable to a wide range of patients.

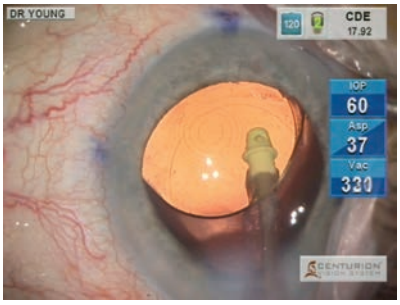

Figure 1. A multifocal intraocular lens, the AcrySof ReStor +3.0 (Alcon), seen in red reflex microscope view following implantation in the capsular bag.

Regarding multifocal IOLs, we now have a wide array of choices from low-add to higher-add models (AcrySof ReStor, +2.5, +3.0, Alcon; and Tecnis Multifocal, ZKBOO, ZLBOO, Abbott) that allow targeting of individual patients' specific vision goals (*Figure 1*). The lower-add IOLs tend to produce fewer problems with optical aberrations and less reduction of contrast sensitivity. A distance-dominant, low-add multifocal design (AcrySof ReStor +2.5 with ActiveFocus, Alcon) has been a welcome recent addition that produces very little degradation of distance clarity. The AcrySof ReStor +2.5 gives us a good alternative for our patients who have an active, outdoor lifestyle who want some near spectacle independence. It may be matched in some patients with a higher-add IOL in the nondominant eye for enhanced near function.

Last year the Food and Drug Administration approved the first multifocal toric IOL (AcrySof ReStor +3.0 Toric). It is available in four models to correct 0.75 to 2.82 D of corneal astigmatism. This development promises to be a great help in enhancing refractive precision in our multifocal patients, but also raises the bar in terms of the importance of accurate IOL placement and postoperative IOL stability.

Intraoperative Aberrometry

Accuracy of IOL selection and precision of toric IOL axis alignment play an increasing role in producing happy cataract surgery patients. Fortunately, we have some effective technologies that assist us in achieving these results. Intraoperative wavefront aberrometry has become an important tool in the operating room for many surgeons. In our facility, we use the ORA system (Alcon), the most commonly used system in the United States, which attaches to the operating microscope overlying the objective lens (*Figure 2*).

While careful preoperative biometry remains important, the ORA readings taken on the aphakic eye following cataract removal and prior to IOL implantation allow the further refinement of spherical IOL power and, importantly, give the surgeon a measurement of aphakic astigmatic power and axis. The real-time digital overlay displayed in the microscope oculars then assists the surgeon in achieving the correct IOL axis placement and takes post-implant readings to assure

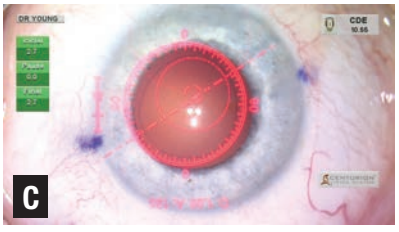

Figure 2. The ORA intraoperative aberrometer (A) attaches over the operating microscope objective. The data interface screen, where the surgeon enters preoperative data and which displays data capture/output, is in the background. The ORA unit in use during a cataract surgery (B). The real-time digital overlay, as seen in the microscope view (C), shows the steep axis of astigmatism and allows real-time guidance of toric IOL axis placement. Note the displayed axis varies mildly from the preoperatively placed ink marks based on preoperative biometry.

optimal IOL placement. Undoubtedly, intraoperative wavefront aberrometry technology will continue to improve and will play an increasing role in helping us provide excellent vision outcomes, especially as IOL technology continues to evolve and requires ever more precise biometry.

Femtosecond Laser-assisted Cataract Surgery

The arrival of femtosecond laser-assisted cataract surgery (FLACS) over the last five years as a viable option for routine cataract extraction continues to spark a debate about whether or not FLACS actually provides improved outcomes or added value over traditional manual cataract surgery. Clearly, femtosecond laser guidance by anterior segment optical coherence tomography in the current generation of lasers produces extremely precise corneal incisions for entry wounds or corneal relaxing incisions, perfectly circular and centered capsulorhexes, and pre-fragmented nuclei to ease subsequent phacoemulsification (*Figure 3, page 20*).

Without doubt, adoption of FLACS requires a large capital investment in equipment, additional costs for supplies and treatment royalty fees and additional time to complete a two-step surgery with a nonsterile laser component separate from a sterile intraocular cataract removal and IOL placement.

These additional costs require that patients pay more for FLACS to make the procedure feasible for surgeons and facilities. Usually, this cost is passed on to patients through premium IOL upgrade fees or enhanced cataract surgery refractive packages aimed at minimizing residual spherical and astigmatic refractive error postoperatively. Practically speaking, many if not most centers offering FLACS do not offer the procedure for routine cataract extraction covered only by insurance-allowable charges.

It was widely assumed at the outset of FLACS adoption that outcomes analysis would ultimately prove that the precision and perfection of laser cuts and probable reduction in necessary phacoemulsification energy translate into better visual outcomes and fewer surgical complications. However, current data are mixed at best and in many cases do not show clear outcomes advantage for FLACS over manual surgery.[1] In some large series, intraoperative complication rates have been marginally higher in FLACS vs. manual surgery.[2,3]

The practical experience of many surgeons points to greater difficulty in certain surgical tasks in FLACS cases, particularly cortical removal. On the other hand, most surgeons agree that the precision of laser-created corneal relaxing incisions is a clear advantage over the manual technique.

Because of the unclear outcomes evidence, extra cost and time/patient-flow constraints, many surgeons—even those with appreciable FLACS experience—remain unconvinced of the added value of the technology and

Figure 3. A femtosecond laser-assisted cataract surgery in progress (A). The applanation cone has been docked on the eye, and the laser incisions are planned and displayed on the viewing screen. Real-time anterior segment optical coherence tomography images confirm accurate incision depth and architecture prior to laser activation. Red reflex microscope image (B) shows a perfectly round laser cut capsulorhexis and presectioned lens nucleus quadrants. Gas bubbles typically form from the laser induced tissue vaporization.

are at least selective about cases for which they use it.

Problematic Pupils

We cataract surgeons have all cringed at the appearance of the occasional cataract referral from our retinal colleagues. You know the one: diabetic, poorly dilating pupil, advanced cataract status post-vitrectomy, maybe a silicone oil fill (now or once present). (We really do appreciate these challenging opportunities!) I murmur to my assistant, "Please make this one a 'last case' of the day," as I exit the exam lane.

The retinal surgeon and cataract surgeon do share some common frustrations with poorly dilating pupils that present difficulties with surgical visualization, as well as the unique challenges that may arise in eyes with considerable prior surgical history.

Indeed, with the ever more common use of alpha-1 adrenergic antagonists in clinical practice, added to the cases of pseudoexfoliation syndrome, diabetic denervation and uveitic synechiae formation, there are days when a surgeon wonders where have all the good pupils gone. Fortunately, we do have some useful tools to employ today that make these tougher cases seem a little easier and more routine.

One very useful recent innovation is the use of intracameral phenylephrine 1% and ketorolac 0.3% (Omidria, Omeros Corporation). Omidria is available as an addition to the infusion fluid during cataract surgery and is FDA-approved for the maintenance of intraoperative pupillary dilation and reduction of postoperative pain. In my own experience, it noticeably improves dilation and maintenance of dilation in cases that in the past would have been more difficult due to loss of an adequate pupil (*Figure 4A*). A recent study by Eric Donnenfeld, MD, demonstrated decreased surgical time, reduced intraoperative complications, reduced use of pupil-expansion devices and improved postoperative best-corrected visual acuity compared to the use of intracameral epinephrine alone.[4] (Dr. Donnenfeld is a consultant to Omeros.)

Certainly, cases still arise where severe floppy iris syndrome or significant posterior synechiae make additional pupil expansion necessary. Convenient preloaded, injectable pupil expansion rings are my go-to solution in these cases. These self-retaining rings (Malyugin rings, available commercially from several manufacturers) may be rapidly placed to maintain a fixed pupil opening during surgery and then rapidly and atraumatically removed following cataract removal and IOL placement (*Figure 4B*). In my own practice, I am using many fewer rings due to increased use of Omidria, in agreement with Dr. Donnenfeld's study.

Infection Prophylaxis

Every cataract surgeon dreads that call from the five-day postoperative cataract patient who was 20/20 and smiling at day one postoperatively and now reports a red, painful eye with very poor vision.

All of our best efforts at state-of-the-art IOL technology, precise and accurate biometry and skilled surgery can be undone by endophthalmitis. This concern has led many surgeons to consider infection prophylaxis

measures that go beyond the traditional Betadine lid prep with topical antibiotic drops given peri- and postoperatively. Increasingly, cataract surgeons are adopting the use of intracameral antibiotic dosing at the completion of a case.

Intracameral Antibiotics

There is convincing evidence from multiple large case series that instituting intracameral antibiotics during cataract surgery markedly reduces the incidence of endophthalmitis.[5,6] A fivefold to tenfold reduction of endophthalmitis risk has been reported.

A variety of intracameral antibiotics have been used, most commonly cefuroxime, moxifloxacin and vancomycin. Indeed, intracameral antibiotic prophylaxis is considered standard of care throughout Europe, where a commercial preparation of cefuroxime for intracameral injection is available (Aprokam, Laboratories Thea).

Increasingly, U.S. surgeons are also adopting intracameral antibiotic prophylaxis. However, some significant barriers have slowed their adoption. The lack of a commercial antibiotic preparation for intraocular use necessitates the use of compounded drugs or the intraoperative preparation of mixed and/or diluted drugs by OR staff. Either circumstance raises the risk of possible contamination or mixing errors as safety concerns.

The intracameral use of commercially available moxifloxacin (Vigamox, Alcon), which is nonpreserved in the bottle and is withdrawn either undiluted or diluted in balanced salt solution, has been well described for over a decade, has been used widely and is without reported problems.[7] Another problem is that current Medicare/third-party regulations require surgeons or facilities to absorb the cost of the antibiotic given as part of a bundled reimbursement, which further increases per-case costs in an era of declining reimbursement.

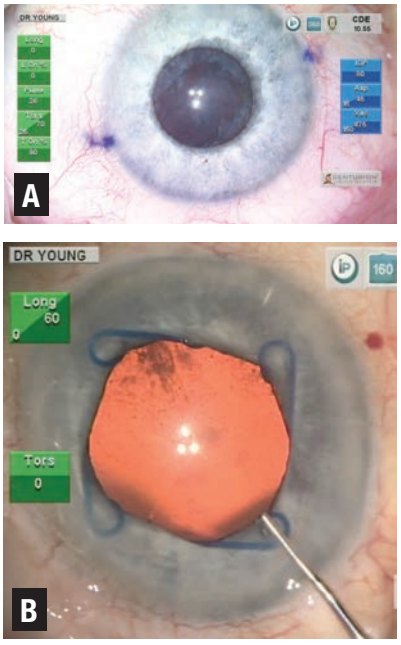

Figure 4. A typical atrophic iris appearance induced by use of tamsulosin (Flomax, Boehringer Ingelheim) (A). In this case, intraoperative use of phenylephrine 1%/ketorolac 0.3% (Omidria, Omeros) in the balanced salt solution infusion helps maintain acceptable pupillary dilation. In the management of floppy iris syndrome (B), a Malyugin ring helps maintain adequate pupillary aperture.

Intravitreal Medications

The frequent difficulties that many of our predominantly elderly surgery patients have with their postoperative eye drop regimens—multiple bottles, multiple and often variable dose frequency, not to mention ever-growing expense—has led many to consider postoperative strategies to reduce or eliminate these regimens.

One common strategy for so-called "dropless" cataract surgery involves the intravitreal injection of 0.2 ml of a compounded formulation of triamcinolone acetonide (15 mg/ml), moxifloxacin (1 mg/ml) and vancomycin (10 mg/ml) (Imprimis Pharmaceuticals) by either pars plana injection or a transzonular infusion using a 30-gauge cannula. In transzonular infusion, a bent 30-gauge cannula is used to traverse the anterior chamber via the cataract incision, then penetrate the zonules via the ciliary sulcus to infuse the drug mixture into the anterior vitreous.[8]

However, anecdotal reports of persistent visual haze and floaters noticeable to patients and retinal complications, including retinal detachments, may deter wider adoption. Alternatively, other "dropless" regimens may simply employ an intracameral antibiotic dose with an injection of sub-Tenon or subconjunctival triamcinolone, avoiding the potential for floaters or vitreoretinal complications. Concern for intraocular pressure rise that may be difficult to control in some patients is a significant negative with these regimens. RS

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A LONG-TERM GAME PLAN FOR NONINFECTIOUS UVEITIS

Treatment requires patience and a nuanced approach.

By Sam S. Dahr, MD

At any major retina meeting, the uveitis sessions usually focus on interesting diagnostic cases, often infections or masquerade syndromes. In day-to-day practice, however, the majority of uveitis cases the retina specialist encounters will be noninfectious and idiopathic in origin. The challenge therefore is not so much diagnosis but executing a proper therapeutic strategy over a time frame measured in years.

Noninfectious uveitis affects approximately 300,000 American adults and 22,000 American children (*Table 1*).[1] Many of these patients are young, and under-treatment early in the disease course can lead to a poor visual outcome that burdens them for decades. In this article, I present a simple yet powerful therapeutic strategy that the retina specialist who does not have a fellowship in uveitis can utilize.

Diagnostic Considerations

Syphilis testing (commonly *Treponema pallidum* IgG antibodies)[2,3] and QuantiFERON testing are recommended for all uveitis patients, as well as a chest X-ray. Additional testing is tailored to the individual clinical presentation. Some specialists say that routine testing for tuberculosis is not indicated if the exam findings are not suggestive (such as serpiginous lesions, choroidal granuloma or occlusive vasculitis). However, QuantiFERON testing is still worthwhile as a precondition for any contemplated systemic immunomodulatory therapy.

If, after appropriate diagnostic testing, a concern lingers for a cryptic infection (such as endogenous fungal endophthalmitis or atypical toxoplasmosis), consider a three-to-six-week trial of oral corticosteroids before any local (periocular or intravitreal) injected corticosteroid. Follow the patient especially closely in the first two weeks of therapy. A worsening of symptoms after the patient starts oral steroids is a signal to revisit the possibility of an infectious uveitis.

If the patient passes the "oral steroid test," a local steroid injection is a next step. Again, any worsening of inflammation immediately after a local steroid injection should flag the possibility of an occult infection. Noninfectious uveitis will typically respond to local steroids for at least several weeks. The disease may recrudesce months later. At this point, discuss systemic immunomodulatory therapy.

Table 1. Prevalence of Noninfectious Uveitis[1]

Per 100,000	Adults	Children
Overall prevalence	121 (117-124.3)	29 (26.1-33.2)
Anterior	98 (94.7-100.9)	22 (19.3-25.4)
Intermediate	1 (0.8-1.5)	0 (0.1-1.1)
Posterior	10 (9.4-11.5)	3 (1.8-4.1)
Panuveitis	12 (10.6-12.7)	4 (2.9-5.6)

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Dr. Dahr is chairman of the department of ophthalmology at Integris Baptist Medical Center, Oklahoma City. He is the founder of the Retina Center of Oklahoma and clinical associate professor at the University of Oklahoma College of Medicine/Dean McGee Eye Institute.

DISCLOSURES: Dr. Dahr reported no financial relationships.

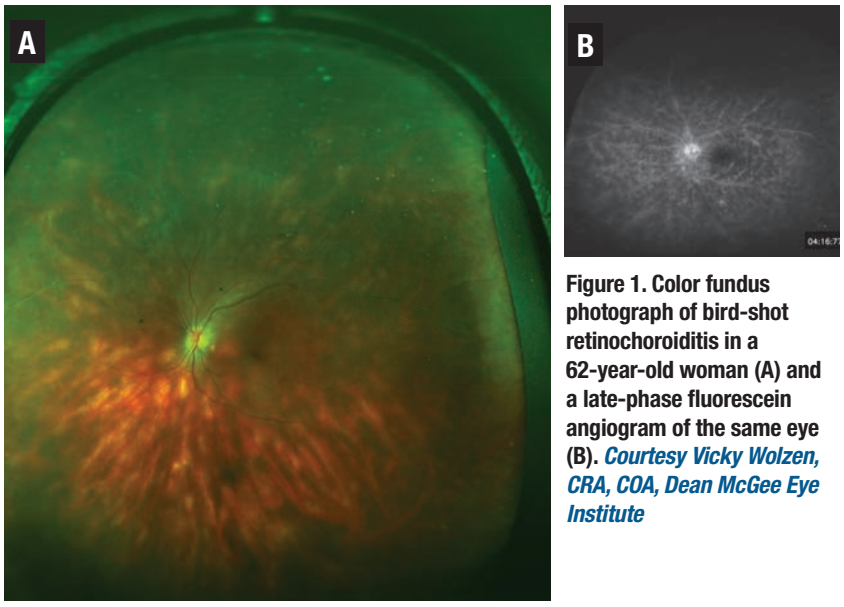

Figure 1. Color fundus photograph of bird-shot retinochoroiditis in a 62-year-old woman (A) and a late-phase fluorescein angiogram of the same eye (B). ***Courtesy Vicky Wolzen, CRA, COA, Dean McGee Eye Institute***

Why Systemic Therapy?

Retina specialists have many good options for local therapy, including periocular triamcinolone, intravitreal triamcinolone, the dexamethasone intravitreal implant (Ozurdex, Allergan), and the fluocinolone acetonide 0.59-mg intravitreal implant (Retisert, Bausch +Lomb).

In addition, intravitreal sirolimus[4] (Santen) is the subject of Phase III trials and has an orphan drug designation in the United States and Europe, and investigational studies are examining an injectable intravitreal fluocinolone acetonide 0.18-mg insert (pSivida).[5] Why take on the "headache" of systemic steroid-sparing therapy?

Many patients have bilateral disease, and keeping these eyes out of the operating room is a laudable goal. Repeated local steroid therapy over the course of years often provokes cataract and glaucoma. Subsequently, surgery for cataract and glaucoma may actually worsen inflammation and lead to anatomic sequelae (synechiae, fibrin deposits on an intraocular lens, anterior vitreous fibrosis and opacity, or macular edema) that further degrade vision—a virtual death spiral of uveitic complications and frustration.

Lessons from MUST Trial

Data from the Multicenter Uveitis Steroid Treatment (MUST) Trial deserves attention. Two arms of the study compared the fluocinolone acetonide implant to systemic immunomodulatory therapy. At 4.5 years, visual acuity outcomes were similar between the two arms.[6,7] Systemic complications were minimal and equivalent between the two arms, but the implant arm showed significant local complications, including cataract, ocular hypertension and need for glaucoma surgery.

Especially for bilateral disease, systemic therapy may be a better first choice given its efficacy and systemic and ocular safety. Recently reported seven-year extended follow-up showed an average 7.2-letter visual acuity advantage of systemic therapy vs. the fluocinolone implant.[8]

From a lifestyle perspective, patients often prefer a regimen of a few daily pills and/or a biweekly subcutaneous injection along with lab testing every two to three months rather than daily drops, periodic peri- or intraocular injections and likely multiple intraocular surgeries (with the attendant complications) over a treatment period that can extend five to 10 years.

Risks of Systemic Therapy

Unfortunately, the perception that systemic medications are "poisons" that consign a patient to future cancer risk or other complications may give some ophthalmologists or patients pause. Thankfully, good data exist. The Systemic Immunosuppressive Therapy for Eye disease (SITE) showed no increased overall or cancer-related mortality in uveitis patients treated with systemic immunomodulatory therapy.[9]

However, a small increased risk of skin cancer may exist, so counsel patients to wear sunscreen and protective clothing, pay attention to any new skin lesions, and undergo a periodic skin exam.[10]

When to Use Systemic Therapy

A pattern of frequent and significant disease recurrence disrupts a patient's life and is often an indication

Take-home Point

Management of noninfectious uveitis demands a therapeutic strategy that can involve systemic therapy, patient counseling, close follow-up, dosing adjustments, combination therapy and consultation with rheumatologists and primary-care providers. Therapy often lasts two years or more. This article reviews corticosteroids, antimetabolites, T-cell inhibitors and biologic agents, as well as challenges of managing noninfectious uveitis in women of childbearing age and children.

Table 2. SITE Study Results[11-13]

Medication	Control at six months	Control at six months with prednisone ≤10 mg	Control at 12 months	Control at 12 months with prednisone ≤10 mg	Discontinuation secondary to systemic side effects at 1 year (event/person-year)	Discontinuation secondary to systemic side effects at 1 year (Kaplan-Meier)	Comments
Methotrexate	63%	37%	74%	58%	Overall 0.13 GI 0.02 BM supp 0.02 Liver enzyme 0.02	Overall 17.5% GI 3.3% BM supp 3% Liver enzyme 3.6%	Less effective for posterior uveitis
Azathioprine	57%	32%	73%	47%	Overall 0.16 GI 0.06 BM supp 0.03 Liver enzyme 0.03	Overall 24.1% GI 10.8% BM supp 3.5% Liver enzyme 4.9%	9% need combination therapy; good intermediate uveitis drug
Mycophenolate	77%	41%	91%	55%	Overall 0.10 GI 0.02 BM supp 0.01 Liver enzyme 0.01	Overall 14.5% GI 3.1% BM supp 2.1% Liver enzyme 1.5%	
Cyclosporine	61%	22%	76%	36%	Overall 0.07 HTN 0.02 Renal 0.02 BM supp 0.001 Liver enzyme 0.006	Overall 10.7% HTN 3.2% Renal 2.5% BM supp 0% Liver enzyme 1.1%	17% need combination therapy; more toxicity at age >55

Key: GI = gastrointestinal; BM supp = bone marrow suppression; HTN = hypertension

for systemic therapy. Classic indicators are anatomic sequelae such as progressive synechiae and iris bombe or angle closure, steroid intraocular pressure (IOP) response, glaucomatous optic atrophy, cataract, vitreous opacity, uveitic macular edema, retinal capillary bed dropout, and macular fibrosis associated with inflammatory choroidal neovascularization.

Other indications for systemic therapy include loss of retinal pigment epithelium with associated peripheral retinal degeneration or bird-shot retinopathy (*Figure 1, page 23*), acute zonal occult outer retinopathy, Vogt-Koyanagi-Harada [VKH] disease) and functional indicators such as visual field loss (*Figure 2*).

Diseases with a known poor prognosis (Behcet's disease, bird-shot retinopathy and VKH) that inevitably smolder and relapse may be treated with systemic steroid-sparing therapy early on, even in the absence of a history of significant recurrence or sequelae.[11] The earlier these severe patients begin systemic therapy, the better they do long term.

A Simplified Approach

The following systemic agents are indicated for infectious uveitis:

- ***Antimetabolites.*** The SITE

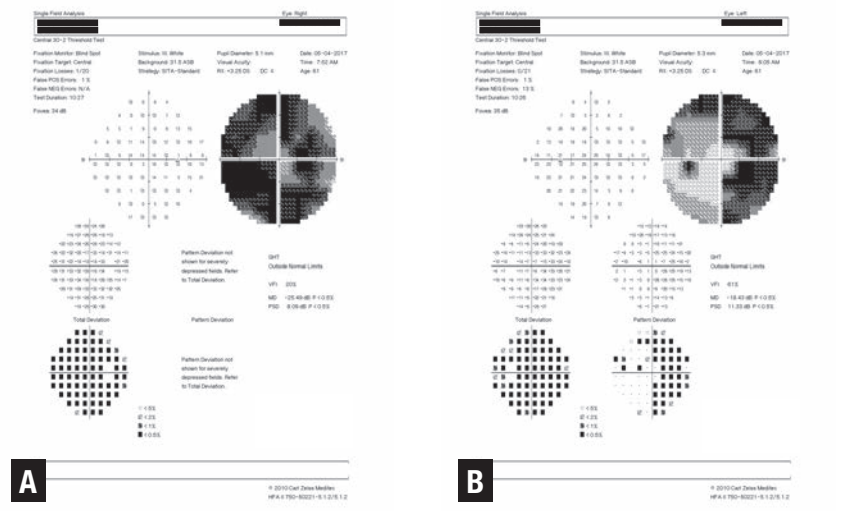

Figure 2. Visual fields of the 62-year-old woman with bird-shot retinochoroiditis in Figure 1 show extensive peripheral loss at the initial presentation. Visual field loss may be an impetus for systemic therapy, even in uveitis patients with good central vision and an edema-free macula.

study examined the use of azathioprine,[12] methotrexate[13] and mycophenolate (*Table 2*).[14] One lesson from the SITE study is that control rates increase from six to 12 months, so you should emphasize patience and a long-term outlook in patient discussions.

The main side effects of antimetabolites are gastrointestinal (GI) upset, bone marrow suppression and liver enzyme abnormalities. GI upset will often improve after one to two weeks of therapy, but some patients will need to discontinue one agent after a couple weeks and try an alternative.

GI upset is idiosyncratic within the antimetabolite family. Some patients may develop symptoms with one agent but not another. Check complete blood count (CBC) and comprehensive metabolic profile (CMP) with a focus on liver enzymes at baseline and after two to three weeks of initial therapy. Thereafter, check labs every two to three months and three to four weeks after any dose increase.

Mycophenolate comes in 250-mg and 500-mg tablets. Typical dosing starts at 500 mg BID and ramps up to 1,000 mg BID in four to six weeks. Maximum dosing is 1,500 mg BID. Mycophenolate is popular among the antimetabolites because it may have a slightly lower incidence of side effects and thus is often the first choice for initial therapy.

Methotrexate comes in 2.5-mg or 5-mg tablets. Methotrexate may also be given as a subcutaneous injection. Regardless, methotrexate is dosed weekly, usually starting at 7.5 to 15 mg per week and then ramping up as needed. Maximum dose is 25 mg per week. Patients should take folate 1 mg the other six days of the week and either dramatically reduce or avoid alcohol intake. Methotrexate is less effective for posterior or panuveitis.

Collaborating With Rheumatologist: Do's and Don'ts

For healthy patients in their 20s, 30s and 40s, you can certainly check CBC, CMP and blood pressure every two to three months. This does not preclude collaboration with a rheumatologist for younger patients, older patients or patients with additional health issues.

Some do's and don'ts with regards to rheumatologist relations bear mention.

- **Do not** send a new uveitis patient to a rheumatologist and say "work this patient up." The ophthalmologist has the benefit of the eye exam, which allows the development of a proper differential diagnosis. Rheumatologists understandably become frustrated at being referred a generic "uveitis" patient and being left in the position of ordering a broad, non-targeted, low-yield workup.
- **Do** order a targeted diagnostic workup before sending the patient to the rheumatologist.
- **Do not** copy the rheumatologist on an electronic medical record (EMR)-generated note and expect her or him to decipher "1+ cell, 2+ cell," etc., and subsequently decide whether dosing should increase or decrease.
- **Do** send a letter or customized EMR note with every visit. Summarize the inflammatory findings of the patient's eye exam in clear terms: "Patient doing well and regimen should be left as is"; or "Patient has some inflammatory breakthrough; in the short term I will undertake some limited local steroid therapy, but could you consider increasing the patient dosage of [name of steroid sparing agent] or adding [name of second steroid sparing agent]?"; or "Patient has now been quiet for two years, could you consider an incremental dose reduction of [name of steroid sparing agent] as part of a long term taper schedule?"
- **Do** suggest specific agents and dose ranges. Always state when the patient's next ophthalmic assessment will take place.

Our metrics—the ophthalmic exam, angiogram, optical coherence tomography and visual field—are more powerful than any blood test the rheumatologist can order to monitor disease response. We bear decision-making responsibility for these patients.

Azathioprine is available in 50-mg tablets. Dosing is based on body weight; 1-3 mg/kg/day, which usually translates to starting at 50 mg daily and increasing to 100 mg or 150 mg a day over the first one to three months. Avoid this medication in gout patients on allopurinol because it can magnify the bone marrow side effects. Azathioprine is a good intermediate uveitis drug and a decent posterior/panuveitis drug (*Figure 3, page 26*).

• ***T-cell inhibitors.*** Cyclosporine (Gengraf, AbbVie; Neoral and Sandimmune, Novartis) is a T-cell inhibitor with a slightly different side effect profile than the antimetabolites. I suggest avoiding Sandimmune, an older formulation. Tablets come as 100 mg or 25 mg. Dosing starts around 2 mg or 3 mg/kg daily and can go up to 5 mg/kg, typically ending up around 150-300 mg daily total. A good starting dose for most patients is often 100 mg BID.[15] For treatment of uveitis, unlike organ transplantation, checking blood levels is not necessary.

Principal concerns with cyclosporine are renal toxicity, hypertension, liver enzyme abnormalities, low magnesium, elevated lipids and paresthesias. The side effect profile for cyclosporine is better than most physicians acknowledge. The drug tends to be well tolerated in patients younger than age 55 and can be used in older populations with close monitoring.

Patients should avoid heavy use of NSAIDS because they may magnify renal toxicity. Recommend frequent blood-pressure checks and ask patients to keep a log. Check blood

count, blood chemistry with attention to serum creatinine and calculated creatinine clearance, and magnesium every one to two months initially and every two to three months thereafter.[16] Patients should also have lipid profiles once or twice a year.

Tacrolimus (Prograf, Astellas) is a T-cell inhibitor with a side-effect profile and monitoring regimen similar to cyclosporine. While cyclosporine has a longer history for treatment of uveitis, tacrolimus may have a slightly lower incidence of kidney and blood-pressure issues.[17] Conservatively, dosing ranges from 0.05 mg to 0.10 mg/kg daily. Tablets come in 1-mg size. Patients often started at 1 mg BID and may go up to 3 mg BID.

• ***Biologics.*** Infliximab (Remicade, Janssen), given as an intravenous infusion every four to six weeks, had been the prototypical anti-tumor necrosis factor (TNF) agent utilized for uveitis.[18,19] Adalimumab (Humira, AbbVie), an anti-TNF agent that the patient typically self administers biweekly as a subcutaneous injection, has become a popular and effective option for uveitis, especially since the FDA granted it a labeled indication for noninfectious uveitis.[20,21] Adalimumab is the only systemic non-corticosteroid agent FDA-approved for the treatment of noninfectious uveitis.

Anti-TNF agents may be considered as first-line therapy for Behcet's disease and as second-line agents for other presentations of uveitis.[20] In practical terms, these agents are often used in combination with an antimetabolite when antimetabolite monotherapy shows some response but greater efficacy is needed.

Adalimumab is given as an 80-mg initial dose followed by 40 mg one week later and subsequently 40 mg biweekly. Patients should have negative QuantiFERON testing before they start therapy because the agent may reactivate latent tuberculosis infections. The retina subspecialist would do well to consult with a rheumatologist in prescribing and monitoring infliximab and adalimumab. These medications are mainstays in rheumatology.

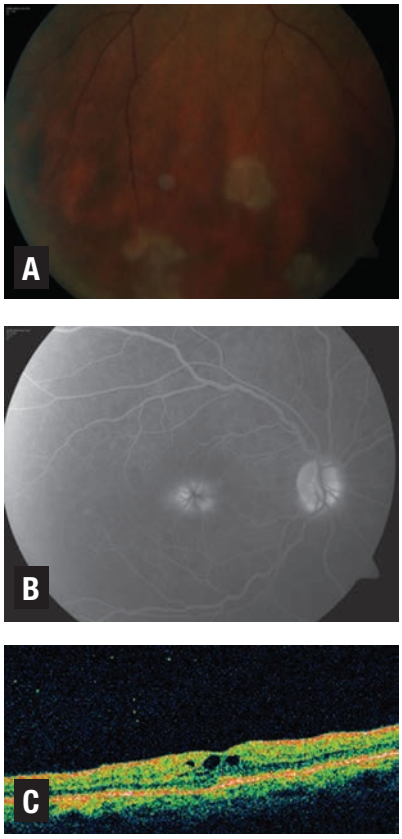

Figure 3. Intermediate uveitis in a 63-year-old woman showing "*taches de bougie*," or "candlewax drippings" (A). Fluorescein angiogram (B) shows late hyperfluoresence consistent with uveitic macular edema, and optical coherence tomography (C) shows prominent foveal cystoid spaces. Her pulmonary function studies were strongly suggestive of sarcoidosis, but she did not pursue lung biopsy. After local steroid therapy and four years of azathioprine therapy, her disease went into remission and she was successfully tapered off azathioprine. ***Courtesy Retina Center of Oklahoma***

Initial Drug Choice

An element of personal style shapes initial drug choice. In the last several years, mycophenolate has become increasingly popular as a first drug in all adult age groups. For intermediate uveitis, mycophenolate or azathioprine are good first-line choices. In young patients with significant posterior uveitis or panuveitis, cyclosporine either alone or in combination with mycophenolate or azathioprine is a good first choice. In older patients, the antimetabolite alone can be initiated. In children, methotrexate is often the first drug of choice.

Patient Counseling

Advise patients to be careful about sun exposure and to use sunscreen. They should also avoid live vaccines. While rare, any patient on immune suppression has a risk of John Cunningham virus-associated progressive multifocal leukoencephalopathy. Consult a neurologist if any new onset neurological symptoms develop.

Pregnancy-related Issues

Women of child-bearing age with uveitis that requires immunomodulatory therapy should be counseled on the need for proper contraception. Generally a hormonal method (eg, oral tablet or a depot injection) is inadequate, and patients typically are advised to use a second method concomitantly, usually a barrier method.

For retina specialists, communicating to the patient's obstetrician-gynecologist or family doctor on the need for proper contraception associated with immunomodulatory therapy is typically sufficient. Verify with the patient on subsequent visits that she is compliant with the ob-gyn's recommendations.

When women with uveitis wish to become pregnant, systemic thera-

py should be tapered to end at least three months before attempting conception. Despite some discussion that agents like cyclosporine may be used in pregnancy, generally these patients should avoid immune suppression because pregnancy itself may have some immune-suppressive effects. Topical, injected or oral steroids can often manage flares during pregnancy.

Children with Uveitis

A significant body of literature supports the use of systemic immunomodulatory therapy in children with uveitis.[22,23] Children present special medical issues and dosing considerations, so collaboration is important—either with a pediatric rheumatologist, a pediatrician familiar with systemic therapy or an adult rheumatologist comfortable managing children.

Children usually tolerate systemic therapy quite well, so such therapy should be initiated early in the disease course. Conversely, local steroid injections in children often quickly stimulate steroid-related cataract and ocular hypertension, prompting surgery that may provoke additional inflammation and anatomic complications, causing a downward clinical spiral. Local steroid injections have a role for treatment of uveitis in children, but they should be used judiciously and sparingly.

In the setting of macular edema, a three-to-six week course of oral steroids (dosed at 0.5 mg to 1 mg/kg daily) will often treat the macular edema in the short term and avoid the need for a steroid injection. Short-term oral steroids generally carry a lower risk of cataract and glaucoma than an injection. The use of oral steroids in such fashion allows time for systemic therapy to start to take effect.

In children with pars planitis, the pars plana membrane will involute slowly over one to three years. Look for less localized haze overlying the membrane, a more gray and less white coloration to the membrane, and decreasing thickness of the membrane. Vitreous cells often persist at the 1 to 2+ level in these patients, raising the question if the medication is having its intended effect.

Again, patience is key. If the anterior chamber is quiet, the central vitreous is free of significant haze, and no macular edema is evident, the patient is likely moving in the right direction, even with some vitreous cell and a membrane that changes only slowly. As the membrane settles down and contracts over one to three years, the patient may develop some tractional retinoschisis, which is best observed unless it threatens vision.[24]

Table 3. Schedule for Adjusting Dosing

Agent	Dosage Increase/Decrease
Mycophenolate	500 to 1,000 mg/day
Azathioprine	50 mg/day
Methotrexate	2.5 to 7.5 mg/weekly
Cyclosporine	50 to 100 mg/day

Efficacy and Dose Adjustment

Nothing is perfect; expect inflammatory breakthroughs during systemic therapy, most of which tend to be fairly mild and treatable with topical, injected or oral steroids. The vitreous need not be cell free. In my experience (other subspecialists may disagree), patients may have 1 to 2+ vitreous cell and be "controlled" and stable for the long term: the anterior chamber has ½+ or fewer cells; the vitreous cells, while up to 2+, are relatively fixed in the gel and pigmented; and the eye lacks vitreous haze, significant retinovascular leakage on fluorescein angiography (FA) or anatomic edema on OCT. Vision is typically good and the patient notes the occasional floater but overall good subjective visual function.

Use all available metrics as indicated for the particular disease—exam, OCT, angiogram with sweeps or wide-field FA. For diseases such as birdshot retinopathy, serpiginous choroidopathy, VKH and AZOOR, consider a visual field every 12 months to assess response to therapy. Goldmann fields are ideal but difficult to obtain; typically an automated 30-2 Sita-Standard or a similar test will do. If a patient is lagging in one finding—for example, persistent uveitic macular edema on OCT or recurrent leakage and expansion of inflammatory choroidal neovascularization refractory to anti-VEGF therapy—consider increasing the dose (*Table 3*).

Document the date and magnitude of all dose changes carefully in the chart. The SITE study clearly shows that immunomodulatory therapy takes six to 12 months to take full effect.[9] When increasing the dose, look for a biological signal of some efficacy in approximately three months, but remember the full effect of a dose increase may take six months (even 12) to manifest. Be patient and utilize oral steroids and local steroid injections judiciously to bridge the time for a dose change to take effect. Consider combination therapy as appropriate.

Safety and Dose Adjustment

Most patients on systemic therapy should have a CBC and CMP every two to four months. With regards to antimetabolites, if a lab comes back

TABLE 4. Expert Panel Guideline For Tapering Prednisone[16]

Daily Dose	Taper Schedule
> 40 mg	Decrease 10 mg/week every 1 to 2 weeks
40 to 20 mg	Decrease 5 mg/week every 1 to 2 weeks
20 to 10 mg	Decrease 2.5 mg every 1 to 2 weeks
10 to 0 mg	Decrease 1 mg every 1 to 4 weeks

with a mildly depressed hemoglobin or white blood cell count, or a mildly elevated liver transaminase, do not panic. First, repeat the lab to verify the abnormal value. If the patient is otherwise doing fine, therapy may continue. Otherwise, reduce the dose by a significant increment (*Table 3, page 27*) and subsequently repeat the labs three or four weeks later. If the patient has other nonocular complications or the abnormal labs persist or worsen, consult an internist or rheumatologist.

Patients prone to high blood pressure (older age, family history, overweight, high stress or untreated sleep apnea) may develop some blood pressure elevation on cyclosporine or tacrolimus, but a mild elevation does not rule out use of these medications. Consult the patient's internist. Underlying factors predisposing a patient to high blood pressure can be addressed and anti-hypertensive medication can often be prescribed. Likewise, if a patient on cyclosporine or tacrolimus shows a small bump in serum creatinine, consider an incremental dose reduction with reassessment of the lab values one to two months later.

Immunomodulatory therapy may also continue in the setting of minor systemic infections. As a precaution, counsel patients to have a low threshold for seeing their primary-care doctor when ill, especially when symptoms persist. Primary-care doctors who know that a patient is on immunosuppression may be more prone to prescribe antibiotics for low-grade, community-acquired illnesses. The MUST trial reported a low rate of infections requiring treatment in both the implant and systemic therapy groups.[7] The MUST investigators suggested these infections "were not associated with any lasting consequences" and hence overall mild.[6,7]

The Steroid-Sparing Effect

Many uveitis patients are on prednisone or need prednisone initially, so some suggestions for prednisone use are in order. Do not use the Medrol Dosepak (methylprednisolone, Pfizer); the duration is too short. Prescribe oral prednisone, usually 50 to 60 mg a day in adults (approximately 1 mg/kg/day). Ideally the patient should start a taper within four weeks, with a goal of 10 mg daily or less by three months. An expert panel developed guidelines for tapering prednisone (*Table 4*).[15] Logically, the increment of taper decreases over time.

Chronic oral prednisone requires close attention to sugars, blood pressure and bone density issues. Supplements of calcium 1,000 to 1,500 mg a day and vitamin D3 800 to 1,000 iu a day are recommended.

• ***Going from 10 mg to zero.*** Most patients on adequate systemic therapy will taper to the low teens with regards to oral prednisone, but oftentimes that last 10 mg of prednisone can present a challenge. In difficult-to-wean patients, adopt a slow or "long-tail" taper for that last 10 mg. Decrease by 1 mg every one to two months. Taking a year to get to zero is acceptable in difficult patients. Establish a flare dose.

An example: if a patient on mycophenolate and cyclosporine makes it to 3 mg of daily oral prednisone and then has a mild breakthrough, put the prednisone back up to 10 mg, supplement as needed with local steroids, achieve quiescence again and then resume the taper a few weeks or months later. If the systemic agents are left at the same dose, come down to 4 or 5 mg a day (just above the flare dose) and then leave the patient at that level indefinitely, with the knowledge that such a low dose of chronic oral prednisone is fairly well tolerated. Not all patients will get to zero, but that's acceptable.

Alternatively, at the time of the breakthrough, increase the dose of the steroid-sparing agents. Give that increased dose three to six months to take effect before attempting once again to dip below the "flare dose" and reach zero.

Role of Combination Therapy

As the SITE study demonstrated (*Table 2, page 24*), monotherapy works fairly well, but 20 to 40 percent of patients may need combination therapy, either because of progression or recurrences on monotherapy, a desire for steroid-tapering effect or disease severity. Combination therapy is well tolerated. Toxicity is relatively low, especially in young people, who have the most at stake.

The traditional combination is an antimetabolite (methotrexate, mycophenolate or azathioprine) plus a T-cell inhibitor (cyclosporine or tacrolimus). An increasingly popular combination is an antimetabolite combined with an anti-TNF agent, usually adalimumab. Rheumatologists are

quite comfortable with this combination and can collaborate with you.

Monotherapy often cannot stop difficult diseases such as the vascular dropout of Behcet's disease or the chorioretinal scarring of VKH, sympathetic ophthalmia and serpiginous choroidopathy. Initial combination therapy is indicated in these cases. If the patient does quite well in the first year of combination therapy, one agent can be carefully tapered.

Tapering

If the immunomodulatory regimen has achieved disease quiescence of two years or more, you can consider a taper. The first step is to verify that the patient wants to taper therapy. Not surprisingly, patients enjoy the stability of disease quiescence and may choose to continue a regimen rather than risk a flare up.

The main rule is to proceed slowly. Usually by this time, you've followed the patient for several years and know the individual's disease pattern well.

In the case of combination therapy, taper the weaker agent in a multiagent regimen first—but any toxicity issue takes precedence. Taper in small increments over six to 18 months. If you cannot achieve a full taper, do not view this as a failure; achieving a lower overall long-term dose is in and of itself a success. No shame exists in resuming a previously successful regimen if that's what it takes to preserve long-term vision.

What to Tell Patients

Patients often struggle with a diagnosis of "uveitis." After all, no one else they know has uveitis, and a lack of etiology after extensive medical testing can be frustrating. While the doctor should tell the patient the diagnosis is uveitis, it's often helpful to say, "Uveitis is rheumatoid arthritis of the eye, and we use the same medicines that rheumatologists use in hundreds of thousands of people to treat arthritis."

You may also say, "The immune system can be overactive or autoimmune in any part of the body, for reasons we don't fully understand, and autoimmune eye disease is called uveitis." These explanations allow uveitis patients to relate to the larger and better known group of patients with autoimmune and rheumatologic diseases and often alleviate anxiety.

And lastly for physicians, do not let a lack of etiology delay therapy. Do not hesitate to initiate systemic therapy in lieu of repeated steroid injections. Consider the analogy of transplantation. We've all been asked by a blind patient, "Doctor, is an eye transplant available?" If an ophthalmologist developed a technique of eye transplantation, that surgeon would win every award in our field and be hailed as a hero. No one would question the use of immunosuppressive drugs for "eye transplant patients"—but the use of these immunosuppressive drugs to preserve vision in uveitis patients has a 35-year track record. RS

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TREATMENTS FOR NONINFECTIOUS UVEITIS: OLD DOGS AND NEW TRICKS

Acthar gel re-emerges, suprachoroidal triamcinolone acetonide emerges.

By Christopher R. Henry, MD

Philip Showalter Hench, a physician at the Mayo Clinic, first described the clinical utility of corticosteroids in 1948, when he used cortisone to treat a patient with rheumatoid arthritis, leading to a dramatic clinical improvement.[1-4] His decision to use cortisone arose from his observation, more than a decade earlier, that rheumatoid arthritis improved during pregnancy and in patients with jaundice, conditions in which endogenous steroids are elevated.[2] For this discovery, he was awarded the Nobel prize in physiology and medicine in 1950, along with his co-worker Edward Calvin Kendall, PhD, and Swiss chemist Tadeus Reichstein, PhD.

Shortly thereafter, ophthalmologists started using systemic corticosteroids for the management of uveitis, and several reported cases were published in the literature in 1950.[5-7] Corticosteroid drops and local steroid injections were subsequently developed and utilized. These developments dramatically changed the landscape for treatment of noninfectious uveitis.

Despite the clinical efficacy of systemic and local corticosteroids in the management of uveitis, significant side effects have always been the main limitation for their use. Systemic corticosteroids have well known cardiovascular, dermatologic, endocrine, gastrointestinal, hematologic, immunologic, metabolic, musculoskeletal and psychiatric side effects (*Table, page 33*).[8]

Ophthalmic side effects of systemic and local corticosteroids are all too familiar to ophthalmologists; they include cataract formation, elevated intraocular pressure, central serous chorioretinopathy and susceptibility to opportunistic ocular infections (amoeba, bacterial, fungal, parasitic and viral), amongst others.[8-9]

The options for the use of both local and systemic corticosteroids continue to expand. This article discusses a new method for delivery of local steroids, via a suprachoroidal microinjector, and will also discuss the use of a subcutaneous repository corticotropin gel, an old pharmacologic agent that is re-emerging for use in ophthalmology.

Suprachoroidal Injection

It is an oft-repeated sentiment that the use of local corticosteroids cannot be separated from their frequent side effects of cataracts and elevated intraocular pressure. Clearside Biomedical is developing potential treatments for eye diseases via suprachoroidal administration. To enable this procedure, Clearside has developed CLS-TA, a proprietary microinjector syringe to deliver triamcinolone acetonide via the suprachoroidal space to mitigate these side effects.[10-12]

The microinjector uses a leur-lock attachable 30-gauge microneedle that comes in 900-µm and 1,100-µm

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lengths (*Figure 1*). During the procedure, the needle is held perpendicular to the sclera, approximately 4 mm posterior to the corneoscleral limbus. The needle indents the sclera slightly and enters the suprachoroidal space. Triamcinolone acetonide 4 mg/0.1 mL is then injected slowly over three to five seconds. When the needle is correctly positioned past the sclera, the medication can be infused to the suprachoroidal space without significant resistance (*Figure 2, page 32*).

Pre-clinical rabbit studies have suggested that concentrated amounts of the triamcinolone acetonide were delivered to the retina and choroid with minimal levels of the medication being detected in the anterior chamber, theoretically reducing the risk of elevated IOP and cataract formation or progression.[11]

Clinical Trials of CLS-TA

Results from a Phase I/II open-label study were recently published.[10] This study enrolled nine patients over a 26-week follow-up period. A total of 11 injections were attempted, and eight injections were successful in delivering the drug to the suprachoroidal space. The mean change in IOP was +0.9mm Hg (range: -4mm Hg to +6mm Hg) at 26 weeks, and no patients required IOP-lowering medications. One patient developed a cataract, but the medication was not successfully delivered in this patient.

The most common reported side effect was transient eye pain, occurring during five of the 11 attempted injections. Two patients had a temporary reduction in vision following the injection. Through week eight, five eyes (63 percent) receiving the injection had achieved a 3-line or greater improvement in visual acuity. Mean visual acuity improvement ranged from 8 to 14 letters gained. Mean reduction in central subfield thickness was 154 µm at eight weeks (range 61-375).

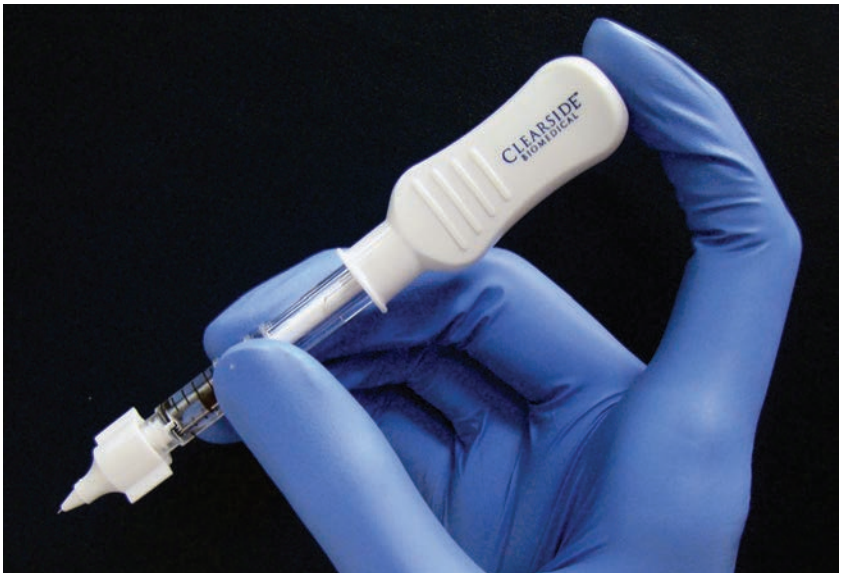

Figure 1. The Clearside Biomedical CLS-TA microinjector uses a leur-lock attachable 30-gauge microneedle that comes in 900-µm and 1,100-µm lengths.

A subsequent Phase II, masked, randomized, controlled multicenter study enrolled 22 patients with macular edema associated with noninfectious uveitis; 17 were randomized to the high-dose arm (4 mg/0.1 mL suprachoroidal triamcinolone acetonide) and five to the low-dose arm (0.8 mg/0.1 mL suprachoroidal triamcinolone acetonide).[12]

The study met its primary endpoint, with subjects in the high-dose arm demonstrating a reduction in macular edema (164 µm, p=0.0017) through two months of follow-up. These patients also showed a statistically significant mean improvement in visual acuity (9.2 letters, p=0.0004).

Eye pain was again the most common ocular adverse event, occurring in three of 17 subjects. One patient had a temporary increase in IOP at the time of injection, but no cases of sustained IOP elevations were attributable to the suprachoroidally injected steroid, and no patients required IOP-lowering drops.

A Phase III, randomized-controlled trial for patients with macular edema associated with non-infectious uveitis (PEACHTREE) is currently enrolling patients.[13] Additionally, further safety data are being collected in a Phase III open-label trial (AZALEA).[14]

Take-home Point

Traditional corticosteroids continue to be a mainstay of treatment for uveitis, but some patients have difficulty with the well-documented side effects, ocular and otherwise. Ongoing trials are investigating the use of triamcinolone acetonide via suprachoroidal injection and subcutaneous repository corticotropin gel—the old pharmacologic Acthar—that is returning to use in ophthalmology. This article reviews the existing evidence for these options for managing noninfectious uveitis.

Acthar Gel

One of the original medications that Dr. Hench used in management of his rheumatology patients was the melanocortin peptide, adrenocorticotropic hormone (ACTH).[15-19] Acthar gel (Mallinckrodt Pharmaceuticals) contains ACTH, which acts on the adrenal glands to stimulate the endogenous production of glucocorticoids. The medication also has steroid-independent properties mediated through its binding to five different melanocortin receptors, which are expressed on T-helper cells, T-regulatory cells, macrophages and dendritic cells.

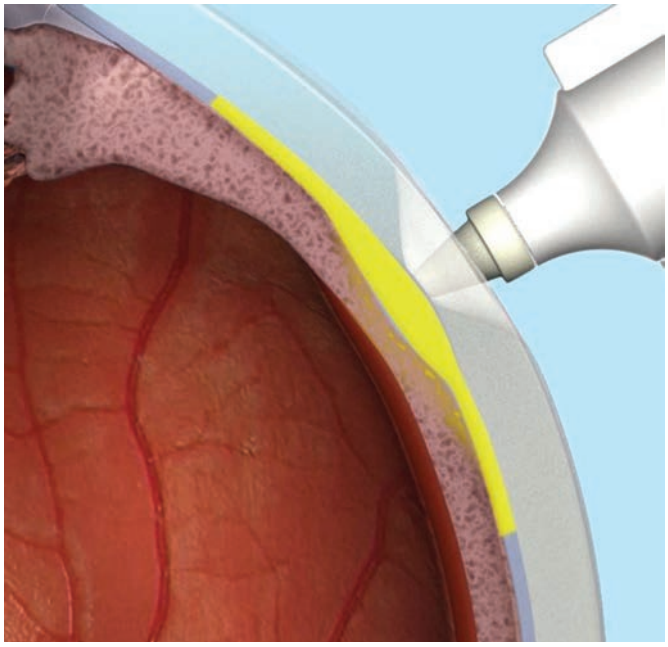

Figure 2. The CLS-TA microinjector needle is held perpendicular to the sclera, approximately 4 mm posterior to the corneoscleral limbus. When properly positioned, the needle can infuse the medication into the suprachoroidal space with minimal resistance.

The melanocortin receptors are also expressed on a number of individual tissues throughout the eye and central nervous system, including retinal ganglion cells and retinal pigment epithelium cells.[19]

The medication is administered subcutaneously or intramuscularly at a dosage of 40 units/0.5 mL or 80 units/1 mL, typically twice weekly. Acthar has been Food and Drug Administration (FDA)-approved for the treatment of anterior uveitis, posterior uveitis and optic neuritis since 1952, but its use has only recently increased.[15-22]

In rheumatology, Acthar has been used mostly as adjunctive therapy in the management of ankylosing spondylitis, dermatomyositis, polymyositis, psoriatic arthritis, sarcoidosis and systemic lupus erythematosus.[16] Neurologists also use Acthar as a primary therapy for infantile spasm as well as acute flares in multiple sclerosis.[16]

A recent retrospective cohort study examined 47 patients with advanced pulmonary sarcoidosis who were treated with Acthar as an alternative to high-dose corticosteroids.[20] Through six months of follow-up,[18] 18 patients (38 percent) discontinued the drug due to side effects (11), cost (four), death (two) or noncompliance (one). Twenty-seven of the remaining 29 patients (93 percent) had improvement of symptoms and/or reduction of oral corticosteroid dosage. Seven had ocular involvement, for which three patients completed a full course of treatment. Four patients discontinued treatment, two because of side effects, one due to cost and one for noncompliance.

Among the patients completing treatment, two had an improvement in uveitis and one remained stable with a reduction in dosage of oral corticosteroids.

Despite Acthar having FDA-approval for the management of uveitis, little has been published about its clinical efficacy for its treatment.[21,22] A case report recently described the successful use of Acthar in a 33-year-old man with unilateral idiopathic panuveitis and retinal vasculitis.[21] The patient was treated with twice-weekly subcutaneous ACTH gel injections over a six weeks; his visual acuity improved from 20/50 to 20/20 in the involved eye. Fluorescein angiography demonstrated a significant reduction in vascular leakage and reduction in vitreous cells and vitreous haze. No significant systemic side effects were noted.

Another report involved the use of Acthar in a 16-year-old girl with a history of refractory uveitis secondary to juvenile idiopathic arthritis.[22] Despite ongoing therapy with methotrexate, infliximab, topical corticosteroids and chronic low-dose oral steroids, the patient continued to have active iridocyclitis and sclerokeratitis. After a trial of toclizumab failed to control inflammation, Acthar 80 units/1 mL twice weekly intramuscularly was added to her treatment regimen.

Within two weeks, the patient's visual acuity had improved from 20/400 to 20/60 in the right eye and from 20/100 to 20/50 in the left eye. At six months, visual acuity had improved to 20/25 in the right eye and 20/20 in the left eye, with complete resolution of iridocyclitis and scler-

Table. Potential Side Effects Of Systemic Corticosteroids

Cardiovascular	Systemic hypertension
Dermatologic	Acne Hirsutism Impaired wound healing
Endocrine	Central obesity Cushingoid habitus Elevated blood glucose Growth suppression Weight gain
Gastrointestinal	Pancreatitis Peptic ulcer
Hematologic	Decreased eosinophils, lymphocytes and monocytes Increased white blood cell count with neutrophilia Hypercoaguable state
Immunologic	Relative immune suppression Susceptibility to infections
Metabolic	Hypernatremia Hypokalemia Water retention
Musculoskeletal	Aseptic necrosis Myopathy Osteoporosis
Psychiatric	Anxiety Depression Euphoria Insomnia Mood swings Psychosis

okeratitis and a reduction in corneal edema. In March, Mallinckrodt initiated a Phase IV trial of HP Acthar gel for treatment of relapsing and remitting multiple sclerosis.[23]

What's Ahead

Corticosteroids will continue to have an important role in the management of patients with uveitis, but their traditional use has been limited by predictable and significant side effects. Forthcoming data will reveal whether the suprachoroidal delivery of steroids can prove efficacious, while limiting local side effects. Further studies on Acthar gel may help determine if this medication should re-emerge as a worthy therapeutic option for patients with uveitis.

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EVOLVING ROLE OF STEROIDS IN RVO AND DME

A deep dive into what clinical trials report on the efficacy of corticosteroids for retinal disorders.

By Hasenin Al-khersan, MD, and Seenu M. Hariprasad, MD

For patients with retinal vein occlusion or diabetic macular edema, the burden of frequent anti-VEGF injections, often monthly, can be difficult to manage. However, corticosteroid implants are an option that can extend therapy to several months, making it easier for patients to comply with the treatment course. Steroids come with their own side-effect profile, most notably increases in intraocular pressure and cataract formation. The retina specialist must weigh the consequences of these adverse events for each patient. This article reviews the clinical trials of corticosteroid therapy in retinal vein occlusion and diabetic macular edema to better equip the retina specialist for making those treatment decisions.

Retinal Vein Occlusion

Retinal vein occlusions (RVO) are the second most common cause of retinal vascular disease after diabetic retinopathy.[1] Occlusions can involve the central retinal vein (CRVO) or hemicentral or branch retinal veins (BRVO). Though not completely understood, occlusions likely lead to a combination of increased venous pressure, production of cytokines such as interleukin-6 (IL-6), and production of vascular permeability factors including vascular endothelial growth factor (VEGF).[2] These processes result in destruction of the blood-retinal barrier. Macular edema (ME) is just one of several devastating complications of RVO that can cause vision loss.

In the past, the Central Vein Occlusion Study recommended observation for ME in CRVO, and the Branch Vein Occlusion Study suggested grid laser therapy for ME in BRVO.[3,4] However, advances in our understanding of disease pathology have led to new therapeutic options, the two main classes of which are anti-VEGF agents and intraocular steroids. The latter is the focus of this review.

Food and Drug Administration-approved anti-VEGF therapies for ME in RVO include ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron) with bevacizumab (Avastin, Genentech) used off label. These treatments target the ischemic component of RVO disease pathology. Trials have also shown steroids to reduce blood-retinal barrier breakdown by inhibiting production of factors like IL-6, VEGF and prostaglandins.[5]

A Paradigm Shift

A paradigm shift in RVO management occurred with the National Eye Institute's Standard Care vs. Corticosteroid for Retinal Vein

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DISCLOSURES: Dr. Hariprasad is a consultant or on the speaker's bureau for Alcon, Allergan, Bayer, OD-OS, Clearside Biomedical, Ocular Therapeutix, Alimera Sciences, Leica, Spark Therapeutics and Regeneron. Dr. Al-khersan has no financial disclosures to report.

Occlusion (SCORE) study. This prospective, randomized trial investigated CRVO and BRVO treated with the standard of care (observation and laser, respectively) vs. intravitreal injection of triamcinolone acetonide (TA) for ME secondary to RVO.[6,7]

The results of the BRVO arm demonstrated no significant differences between the sham and treatment arms in ≥15-letter improvement at 12 months.[6] However, the CRVO arm showed a significant increase in subjects gaining ≥15 letters from baseline at 12 months in the 1-mg and 4-mg TA arms compared to the standard-of-care group (26.5 percent and 25.6 percent vs. 6.8 percent, respectively).[7]

These findings first suggested the utility of steroids in ME due to RVO, signaling a departure from the observational approach to CRVO. TA is commercially available as compounded TA, kenalog and Triesence (Alcon). Intravitreal use of kenalog and compounded TA is off-label, while Triesence and Trivaris (Allergan) are FDA-approved for intraocular use but not specifically for RVO. Although Trivaris was used in the SCORE studies, it is not commercially available.

Drug-delivery methods have also made significant progress. Anti-VEGF agents can be burdensome, often requiring injections every month. Ozurdex (Allergan) is an extended-release dexamethasone-copolymer complex (*Figure 1*). Dexamethasone (DEX) is three times more potent than TA, but its half-life in the eye is less than six hours.[2] However, in a polylactic-co-glycolic acid polymer like Ozurdex, dexamethasone can persist in the eye for up to six months.

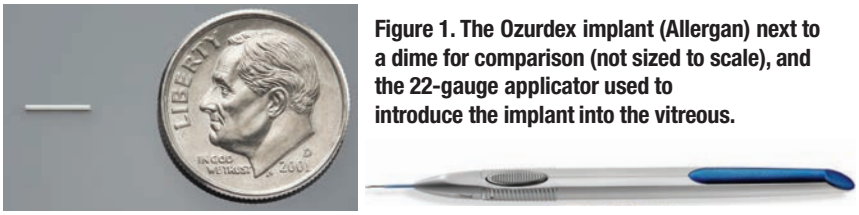

Figure 1. The Ozurdex implant (Allergan) next to a dime for comparison (not sized to scale), and the 22-gauge applicator used to introduce the implant into the vitreous.

The Ozurdex implant is injected into the pars plana with a 22-gauge needle. Ozurdex was FDA-approved in 2009, the first pharmacologic agent specifically approved for ME secondary to RVO.

The GENEVA studies demonstrated the efficacy of Ozurdex in treating ME secondary to RVOs.[8] The studies consisted of two parallel, randomized controlled trials. A total of 1,256 patients were randomized into 0.7-mg and 0.35-mg DEX implant groups and a sham group; 66 percent had BRVO and 34 percent had CRVO. Eyes receiving either DEX dose showed 15-letter improvement in visual acuity significantly faster than the sham group ($p<0.001$). By six months, 41 percent of the 0.7-mg group and 40 percent of the 0.35-mg group had responded with at least a 15-letter gain compared with 23 percent in the sham group.

At day 180, 22 percent of the 0.7-mg DEX group still maintained at least 15-letter improvement, but this did not significantly differ from the sham arm. However, when the six-month analysis excluded patients with visits after day 180, the difference between the 0.7-mg and sham groups was significant (26.4 percent vs. 17 percent, $p=0.017$).[8] Ozurdex is only expected to last six months, which may explain the significance attained by excluding visits after day 180 from the analysis.

GENEVA Study IOP Findings

A concern among physicians when using steroids is increasing intraocular pressure. While the treatment groups in the GENEVA study exhibited significantly more ocular hypertension ($p\leq0.002$), the rise was responsive to topical IOP-lowering therapy in the majority of cases. Only five eyes from the DEX treatment groups required surgery to treat IOP. The trial noted no significant differences in IOP between the treatment arms and sham at six months.[8]

The GENEVA studies also reported extended data at 12 months.[9] After six months, subjects were eligible to receive the Ozurdex injection regardless of the initial treatment group if their visual acuity was <20/20 or central subfield thickness was >250 µm. In patients who received two injections, best-corrected visual acuity (BCVA) gains were similar between the first and second six-month periods (32 percent and 30 percent of subjects, respectively, gained ≥15 letters).

Importantly, 21 percent of BRVO and 17 percent of CRVO patients only needed one implant over a year. Additionally, the safety profile of Ozurdex was similar after the second injection except with respect to cataract formation: 29.8 percent of phakic eyes treated with two 0.7-mg doses developed cataracts while only 10.5 percent of the delayed-treatment group did ($p<0.001$).[9]

Take-home Point

Given the multifactorial nature of macular edema from retinal vein occlusion (RVO) and diabetic macular edema (DME), corticosteroids have become an effective adjunct for treatment. While anti-VEGF agents are approved for both diseases, advances in corticosteroid delivery via inserts are changing how clinicians approach these diseases. This article reviews the evidence that supports corticosteroid use for RVO and DME.

Tailor Therapy Pending Trials

With the availability of both steroids and anti-VEGF agents for ME, retina specialists must decide which therapy to employ. As of yet, there are no published results from randomized controlled trials comparing anti-VEGF agents directly with corticosteroids for RVO.

Trials also need to evaluate combination therapies because future treatment will consist of regimens of both anti-VEGF agents and corticosteroids for many patients. The TANZANITE trial is the first FDA registration trial in RVO investigating combination therapy.[10] This Phase II study examined combination therapy with CLS-TA (Clearside Biomedical), a formulation of TA injected suprachoroidally, with intravitreal aflibercept compared to aflibercept alone in ME secondary to RVO (*Figure 2*).

Early results showed the combination arm needed 60 percent fewer aflibercept injections after initial treatments compared to aflibercept monotherapy (nine vs. 23 injections, respectively, p=0.013). The Phase III study, Suprachoroidal Injection of Triamcinolone Acetonide with IVT Aflibercept in Subjects with Macular Edema Following RVO (SAPPHIRE), is underway.[11]

Until further evidence emerges regarding optimal therapy for ME in RVO, retina specialists must consider the needs of the individual patient. Generally, anti-VEGF treatments are administered first because they lead to quick recovery of vision.

Reassess Treatment Response

Physicians should reassess and react to patients' responses to treatment. In the BRAVO trial of ranibizumab in BRVO, approximately 80 percent of the first-year visual acuity gains and a great majority of the reduction in macular thickness occurred by the third or fourth anti-VEGF injection.[12,13] If by that time the patient shows no improvement, you must consider a different approach.

Partial responders show suboptimal responses in visual acuity gains and persistent ME after monthly anti-VEGF injections for three months. These patients are candidates for combination therapy with Ozurdex alongside the anti-VEGF agent.

Nonresponders who show no improvement from baseline VA, central retinal thickness (CRT) and macular morphology on optical coherence tomography after three months of anti-VEGF injections should start a different anti-VEGF agent, a steroid or a combination of the two.

We are encouraged by the TANZANITE trial results that show more rapid visual recovery and macular drying and decreased injection burden when aflibercept is dosed in combination with CLS-TA compared to aflibercept monotherapy in patients with ME secondary to RVO.[10]

Lastly, the patient's ability to tolerate the treatment burden is critical. Anti-VEGF treatments often require monthly injections, which can be difficult for patients, especially if they're receiving treatment in both eyes. Meanwhile, corticosteroid implants can be effective for several months. Thus, the treatment algorithm must also factor in the patient's ability to adhere to the treatment course to achieving maximal outcomes.

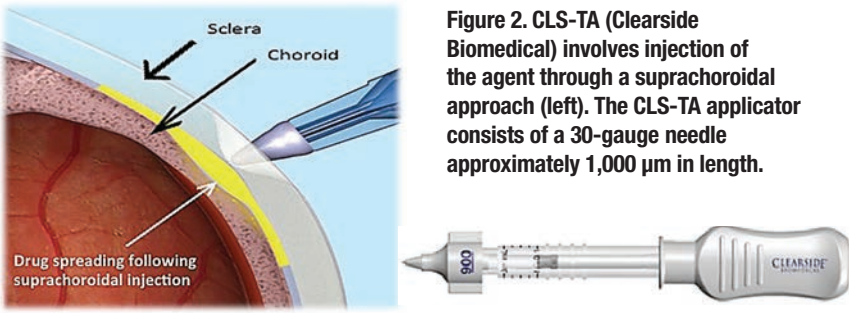

Figure 2. CLS-TA (Clearside Biomedical) involves injection of the agent through a suprachoroidal approach (left). The CLS-TA applicator consists of a 30-gauge needle approximately 1,000 µm in length.

Diabetic Macular Edema

Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide. Vision loss associated with DR is most often due to diabetic macular edema (DME).[14] Capillary leakage, fluid accumulation, and macular thickening occur alongside the breakdown of the blood-retinal barrier. This deterioration leads to the expression of inflammatory factors including vascular endothelial growth factor (VEGF), placental growth factor, and IL-6 and leukocyte migration into the retina.[15,16] For decades, the standard of care for DME was medical management of diabetes along with focal/grid photocoagulation of leaking aneurysms and capillary beds.

The benefit of laser in DME was first shown in 1985 in the Early Treatment Diabetic Retinopathy Study (ETDRS).[17] However, much progress has been made since in the development of pharmacological agents specifically targeting DME. In 2012, ranibizumab became the first FDA-approved pharmacologic treatment for DME, its benefits demonstrated in the RISE and RIDE trials.[18] While anti-VEGF agents have been critical to the treatment of DME, the RISE and RIDE trials also showed that after two years of monthly injections, macular edema >250 µm central

thickness on OCT persisted in 20 to 25 percent of patients.[18] Additionally, approximately 40 percent of subjects did not achieve BCVA ≥20/40.[18] Thus, while anti-VEGF agents have revolutionized the treatment of DME, the need for further pharmacologic treatments remains.

Figure 3. The Iluvien implant (Alimera Sciences) pictured next to a quarter for comparison (not sized to scale) and the 25-gauge applicator used to introduce the implant into the vitreous.

DRCR and Steroids for DME

The Diabetic Retinopathy Clinical Research (DRCR) Network Protocol I study was among the first randomized controlled studies to evaluate the use of steroids for DME.[19] This study randomized eyes into four groups: sham also receiving prompt laser treatment; 0.5-mg ranibizumab group and prompt laser treatment; 0.5-mg ranibizumab with deferred laser treatment; or 4-mg TA with prompt laser. The primary outcome was visual acuity at one year.

The one-year mean change in letter score from baseline relative to sham was significantly greater in the ranibizumab-prompt laser and ranibizumab-deferred laser groups (+9 letters for each, $p<0.001$), but not in the TA-prompt laser group (+4, $p=0.31$) vs. the sham-prompt laser group (+3).

However, in a subanalysis of 273 pseudophakic eyes at baseline, visual acuity improvement in the TA-prompt laser group was comparable to that in the ranibizumab groups, suggesting that the visual acuity outcomes might have been influenced by cataract formation. This observation was supported by the fact that the TA-laser group, like the ranibizumab groups, exhibited statistically significant, decreased retinal thickening relative to sham.

While the results of the Protocol I study were not definitive regarding the use of TA in DME, the MEAD trial evaluating Ozurdex demonstrated the utility of steroids in DME.[20] The MEAD study consisted of two randomized sham-controlled Phase III trials of 1,048 patients with DME. Patients were assigned to DEX 0.7-mg, DEX 0.35-mg and sham groups. Subjects were followed for three years and treated with Ozurdex no more than every six months.

The percentage of patients with ≥15-letter improvement in BCVA from baseline at year three or final visit was greater with DEX 0.7 mg (22.2 percent) and DEX 0.35 mg (18.4 percent) than with sham (12 percent; $p\leq 0.018$). Among phakic study eyes at baseline, the incidence of cataract-related adverse events was 67.9 percent, 64.1 percent and 20.4 percent (with 59.2 percent, 52.3 percent and 7.2 percent undergoing cataract surgery) in the DEX 0.7-mg, DEX 0.35-mg and sham groups, respectively.

Approximately one-third of patients in the DEX groups had significant increases in IOP requiring topical medication with returns to baseline by six months after each DEX implant. Only three patients in the DEX groups combined required trabeculectomy to manage IOP.[20]

Sustained-release FA

Another steroid studied for DME is fluocinolone acetonide (FA). Iluvien (Alimera Sciences) is a nondegradable sustained-release FA intravitreal insert introduced into the vitreous with a 25-gauge applicator (*Figure 3*). The FAME trial evaluated the use of Iluvien in DME. This was a parallel, three-year Phase III trial with 953 patients.[21] The arms were a sham group, a 0.2-mg FA group and a 0.5-mg FA group. The percentage of patients with improvement of ≥15 letters from baseline at 24 months was 28.7 percent and 28.6 percent in the low- and high-dose FA groups, respectively, compared with 16.2 percent in the sham group ($p=0.002$ for each).

Among phakic eyes, the rates of cataract surgery were higher in the treatment arms with 74.9 percent of the low-dose group, 84.5 percent of the high-dose group and 23.1 percent of the sham group requiring cataract surgery. Incisional glaucoma surgery was performed in 8.1 percent of the high-dose group, 3.7 percent of the low-dose group and 0.5 percent of the sham group. We should note that the FDA label for Iluvien mitigates the risk of ocular hypertension by mandating that this implant be used only in DME patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP. Adhering to the FDA label indications significantly reduces the risk of IOP rise after Iluvien administration.[22]

Iluvien is not to be confused with Retisert (Bausch + Lomb), an implant sutured to the anterior wall of the eye that releases FA into the anterior vitreous. Some investigators have drawn conclusions regarding the side-effect profile of Iluvien but referenced data

from Retisert trials in noninfectious uveitis, for which it is FDA-approved, and not DME, for which Retisert is not approved.[23] Studies of Retisert in DME found the insert caused significant reduction in edema, but about 20 percent of treated subjects required surgical treatment for elevated IOP at 24 months.[24] Iluvien and Retisert differ both in their delivery and side-effect profiles and have not been evaluated head-to-head.

As with RVO, no randomized controlled trials have yet evaluated steroids and anti-VEGF agents head-to-head or in combination for DME. CLS-TA, as previously mentioned, is a TA formulation administered suprachoroidally. Phase I and II trials evaluating suprachoroidal CLS-TA with intravitreal aflibercept vs. suprachoroidal CLS-TA monotherapy for DME are under way.[25] Until such studies are completed, retina specialists must tailor treatment to the individual patient.

When to Add Steroid Therapy

Anti-VEGF agents are undoubtedly first line for the vast majority of patients. However, as with RVO, the response to these agents requires constant re-evaluation. In the DRCR Protocol T trial, 34 percent of aflibercept subjects, 64 percent of bevacizumab subjects and 42 percent of ranibizumab subjects had >250 µm macular thickness at 12 months in spite of receiving 10 injections.[26]

In patients with partial responses at three months, retina specialists should consider the addition of a steroid such as Ozurdex or Iluvien. The patient's comorbidities must also be factored in. A patient without glaucoma is a good candidate for earlier intervention with a steroid treatment. A patient with severe glaucoma who is not responding to an anti-VEGF agent may warrant a trial with a different anti-VEGF treatment before a steroid treatment is introduced. As with any medical treatment, understanding the broader medical and social context of the patient is critical to successful therapy.

In sum, the proliferation of treatment options for macular edema in RVO and diabetes has led to great improvements in outcomes. Many patients who would have otherwise been blinded are maintaining their vision. However, with an increasing number of therapies and little rigorous data comparing them as of yet, retina specialists are left to discern the best regimen for each patient.

Steroids offer a promising treatment class for macular edema that can be of great benefit to patients who do not respond optimally to anti-VEGF agents or cannot comply with the frequency of anti-VEGF treatment. Steroids come with their own side-effect profile, most notably increases in IOP and cataract formation. Retina specialists must weigh the consequences of these adverse events individually for each patient as their impact depends on patients' underlying comorbidities. Ultimately, steroids are an effective adjunct in the treatment of macular edema from RVO and DME given the multifactorial nature of these diseases.

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PIPELINE FOR NEOVASCULAR AMD RUNS FULL

An update on small-molecule anti-VEGF agents, anti-angiopoietin-2 antibodies, topical drops and port delivery.

By Arshad M. Khanani, MD, MA, P. David Freeman, MD, Greggory M. Gahn and Sarah Stanko

Despite the tremendous success of anti-VEGF therapy to treat wet age-related macular degeneration, patients are experiencing increased treatment burdens due to frequent injections that require multiple office visits to assess their response. Retina specialists know well that this can be demanding for patients and ultimately result in decreased patient adherence, an inconsistent level of treatment and poorer visual acuity outcomes in the real world compared to clinical trials.[1]

Here, we explore emerging treatment modalities for wet age-related macular degeneration that aim to overcome the shortcomings of existing anti-VEGF agents by providing sustained improvement of vision while reducing the frequency of injections and clinic visits.

Brolucizumab

Formerly known as RTH258 and ESBA1008, brolucizumab (Novartis) is a humanized antibody fragment with a molecular weight (26 kDa) much smaller than that of any currently available anti-VEGF agent.[2] Investigators have proposed that the smaller molecular weight of brolucizumab may result in greater ocular tissue penetration and higher concentrations of the drug being localized in the retina.

Animal studies have elucidated these benefits, having shown a fourfold lower systemic exposure compared to ranibizumab (Lucentis, Genentech), a tolerability to higher doses and a high affinity for

Take-home Point

Anti-VEGF therapies will continue to remain the treatment of choice for age-related macular degeneration for many years to come, but emerging advancements in newer smaller anti-VEGF molecules, combination therapies and delivery systems have shown promise in reducing the frequency of injections and improving visual outcomes in patients with neovascular AMD. This article reviews five new agents and one drug-delivery system now in trials that strive to achieve those goals.

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Ms. Stanko is a third-year medical student and Mr. Gahn a second-year medical student at the University of Nevada School of Medicine.

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TABLE: The Pipeline for Neovascular AMD Therapies

Molecule	Company	Mechanism of Action	Route of Delivery	Phase	Expected Completion
Brolucizumab	Alcon	Humanized antibody fragment, anti-VEGF agent	Intravitreal	III	Mid 2018
Abicipar	Allergan	Ankyrin repeat protein, anti-VEGF agent	Intravitreal	III	Mid 2019
RG7716	Roche/ Genentech	Bispecific monoclonal antibody that binds VEGF-A and Ang2	Intravitreal	II	Late 2017
Nesvacumab	Regeneron	Fully human monoclonal antibody that binds Ang2	Intravitreal	II	Late 2017
Ranibizumab Port Delivery System (RPDS)	Roche/ Genentech	Provides constant levels of monoclonal antibody that binds VEGF-A	Placed beneath conjunctiva	II	Ongoing
Squalamine Drops	Ohr Pharmaceutical	Novel drop inhibits VEGF, PDGF and bFGF.	Topical	III	Late 2017

Key: VEGF = vascular endothelial growth factor; Ang2 = angiopoietin 2; PDGF = platelet-derived growth factor; bFGF = basic fibroblast growth factor

vascular endothelial growth factor.[3] Early human studies in patients who have been diagnosed with neovascular AMD have shown promising results, reporting that a single dose of brolucizumab may be more potent and longer lasting than a single dose of ranibizumab.[4] Phase II studies comparing brolucizumab to aflibercept (Eylea, Regeneron) have shown noninferiority, providing the basis for the ongoing phase III studies, HAWK and HARRIER. These studies are fully enrolled with an estimated completion time of mid-2018.[5]

Abicipar

Abicipar (Allergan), formerly AGN-150998, is a designed ankyrin repeat protein (DARPin) that acts as an anti-VEGF agent. Abicipar has small-molecular weight structure with the added benefit of having a polyethylene tail designed to provide the drug with a longer intravitreal half-life.[6] During the Phase II REACH study, 25 patients were randomized to abicipar 1 mg, 23 patients to abicipar 2 mg, and 16 patients to ranibizumab 0.5 mg.

Results from this study showed an improvement of mean visual acuity from baseline of 9 letters for abicipar 2 mg and 7.1 letters for abicipar 1 mg compared to 4.7 letters for ranibizumab 0.5 mg.

Although this study was not powered to show statistical significance, it provided promising results that paved the way for a Phase III program consisting of two trials: CEDAR and SEQUOIA.[6] These randomized, double-masked studies comparing abicipar to ranibizumab have each recruited 900 patients and are fully enrolled. The estimated completion date is mid-2019.[7]

RG7716

RG7716 (Genentech) is a bispecific monoclonal antibody that uses CrossMab technology to bind VEGF-A on one arm and angiopoietin 2 (Ang2) on the other arm. Ang2 plays a role in suppressing phosphorylation of Tie2 (Tyrosine kinase with immunoglobulin-like and epidermal growth factor like domains 2) receptor.

Tie2 receptor is phosphorylated in the active state and has been implicated in the modulation of vascular permeability. Upregulation of Ang2 has been observed in proangiogenic conditions such as diabetic retinopathy, diabetic macular edema, AMD and retinal vein occlusion leading to decreased Tie2 activation and subsequent vascular leakage and neovascularization.[8-10]

A Phase I study in patients with difficult-to-treat neovascular AMD deemed RG7716 "safe and well-tolerated" among those with no observed dose-limiting toxicities or unexpected adverse events.[11]

During the Phase I study, patients were divided into two treatment groups: a single ascending-dose group that received 0.5-, 1.5-, 3- and 6-mg doses of RG7716; and a multiple ascending-dose group that received three monthly treatments each with 3- and 6-mg doses.

The single ascending-dose group documented a median improvement in visual acuity of 7 letters, while the multiple ascending group had a median improvement of 7.5 letters.[11]

A randomized, double-masked Phase II study, AVENUE, is looking at efficacy of RG7716 vs. ranibizum-

ab in the treatment of choroidal neovascularization secondary to AMD. AVENUE is fully enrolled and has an estimated completion by the end of the year.[12]

Another randomized Phase II trial looking at extended dosing interval with RG7716, STAIRWAY, is also fully enrolled and is expected to finish in first quarter of 2017.[13]

Nesvacumab/ Aflibercept

Nesvacumab (Regeneron) is a fully human monoclonal antibody that inactivates Ang2 with high affinity. In combination with an anti-VEGF agent, such as aflibercept (Eylea, Regeneron), nesvacumab has the potential to prevent the pathological process of angiogenesis in neovascular AMD.

The Phase I study evaluating the safety and tolerability of nesvacumab/aflibercept in 20 patients with neovascular AMD or DME reported visual and anatomical improvements at all dose levels.[14] This trial reported no dose-limiting toxicities, ocular inflammation or unexpected systemic effects.

These results have led to a Phase II study (ONYX), now fully enrolled, that will assess the efficacy of intravitreal nesvacumab/aflibercept compared to aflibercept in patients with neovascular AMD.[15] Estimated completion date for ONYX is by the end of the year.

Ranibizumab Port Delivery

The ranibizumab port delivery system (RPDS, Genentech) is a port placed beneath the conjunctiva that physicians can refill with a custom refill needle.[16] The device is designed to release ranibizumab over a period of months, potentially reducing the burden of frequent injections.

An implantable delivery system like this has the potential to provide patients with a constant level of treatment and ultimately become a tool to better manage neovascular AMD and improve long-term visual outcomes.

The Phase I study showed RPDS to be well-tolerated with documented improvement in best-corrected visual acuity compared to monthly injections.[17] Genentech has received fast-track designation from the Food and Drug Administration and has initiated a randomized, double blind, Phase II study (LADDER) that is currently under way.[18] LADDER will assess the efficacy and safety of the delivery system.

Squalamine Drops

Squalamine (OHR Pharmaceutical) is a topical anti-angiogenic drop with a novel intracellular mechanism of action. The drop works by inhibiting multiple growth factors, including VEGF, platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF).

The topical formulation of Squalamine, called OHR-102, is currently being evaluated in Phase III trial. The MAKO study, is a multicenter, randomized, double masked, placebo controlled clinical trial looking at monthly ranibizumab and either Squalamine drops or placebo drops twice daily.[19] The study is fully enrolled and data is expected in early 2018. RS

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Surgery for GRT Detachments

Updated approaches involve vitrectomy, lasers, direct PFCL-to-silicone oil (SO) exchange and more. ***By Rachel Trussart, MD, FRCSC, Peng Yan, MD, FRCSC, and Efrem D. Mandelcorn, MD, FRCSC***

Treatment of rhegmatogenous retinal detachment associated with giant retinal tear, defined as a full-thickness retinal break extending three clock hours (90°) or more circumferentially, remains more challenging than conventional primary rhegmatogenous retinal detachment (RRD) with smaller breaks.

In a giant retinal tear (GRT), the vitreous is firmly attached to the anterior edge of the tear while the posterior flap is free from any vitreous attachment, allowing it to scroll and roll toward the posterior pole. The presence of posterior vitreous detachment (PVD) further increases the propensity for flap mobility and subsequent tear inversion.[1]

RRD related to GRT has always been a surgical challenge for vitreoretinal surgeons because of the increased risk of retinal slippage, redetachment and proliferative vitreoretinopathy (PVR). Over the years, however, authors have described several approaches that can improve outcomes. Here, we present an up-to-date review of GRT with RRD, looking at the common issues surgeons encounter and some of the current thinking about management.

Vitrectomy

The use of preservative-free triamcinolone (Triesence, Alcon) is helpful in confirming intraoperative PVD and performing a complete vitrectomy. Take care to ensure that all vitreous attachments are released from the posterior and anterior flap tear. Under scleral indentation, perform a meticulous 360° shaving of the vitreous base anteriorly. Trim the anterior flap of the GRT entirely to prevent anterior peripheral traction, PVR and possibly peripheral ischemia.

Rolls and Folds

Perfluorocarbon heavy liquid (PFCL) is very useful for unfolding the posterior retinal flap in a GRT RRD. Gradually inject the PFCL as a single bubble over the optic disc, keeping the cannula tip within the PFCL bubble as it expands in size (*Figure 1*).

Inject the PFCL until it fills to the posterior edge of the GRT, allowing the GRT flap to unfold. It is important to inject the PFCL slowly under low infusion pressure to avoid too much turbulence and secondary multiple PFCL bubbles. We typically turn the infusion down to 5 to 10 mmHg and also use a dual-bore cannula (MedOne Surgical) to avoid this complication.

In cases of a persistent inverted or rolled GRT, you can use the soft-tip PFCL injection cannula to unfold the scrolled retina, but this may inadvertently lift the GRT edge and lead to subretinal PFCL. We've found that gently brushing the folded GRT with the Tano diamond-dusted membrane scraper avoids lifting of the tear and lowers the chance of inducing subretinal PFCL (*Figure 2*).

View the Video

Drs. Trussart, Yan and Mandelcorn demonstrate their technique for giant retinal tear surgery in this video. Available at: bit.ly/RS_GRT_003.

Laser

We routinely apply two confluent rows of laser in a continuous mode along the posterior edge of the GRT followed by three rows of scattered laser posterior to these. Pay special attention to treating the horns of the GRT with broader laser up to the ora serrata to prevent any guttering of subretinal fluid and recurrent RRD postoperatively.

An illuminated endolaser probe is helpful for ensuring that all edges of the tears are treated. We often proceed with 360° endolaser photocoagulation in two or three rows posterior to the ora serrata in cases of GRT and RRD.[2]

Retinal Slippage

Slippage occurs with incomplete drainage of subretinal fluid posterior to the GRT, causing reattached retina and the GRT to slide toward the posterior pole. To prevent aqueous entry into the subretinal space during this process with subsequent retinal slippage, we proceed with a slow air-fluid exchange in a stepwise anteroposterior direction.

Before aspirating PFCL, first meticulously and slowly drain all subretinal fluid anterior to the PFCL meniscus (*Figure 3*). Perform an air-fluid exchange by placing the tip of the extrusion cannula anterior to the GRT above the PFCL meniscus to ensure complete drainage of subretinal fluid.

Direct PFCL-to-silicone oil (SO) exchange can also reduce the likeli-

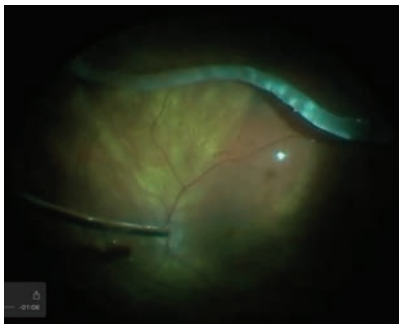

Figure 1: Perfluorocarbon heavy liquid (PFCL) is slowly injected as a single bubble over the optic disc, keeping the cannula tip within the PFCL bubble as it expands in size, to unfold the giant retinal tear.

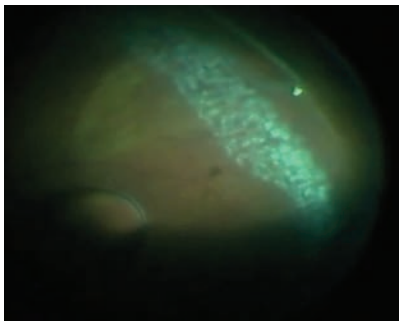

Figure 2: The rolled giant retinal tear (GRT) edge is gently brushed with a Tano diamond-dusted membrane scraper. This technique allows for easy unfolding of the GRT even when the edges of the retina are stiff and adherent.

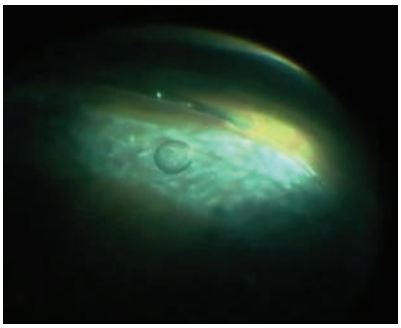

Figure 3: Meticulous, slow drainage of subretinal fluid anterior to the perfluorocarbon heavy liquid meniscus at the onset of the fluid-air exchange avoids slippage.

hood of retinal slippage because of the hydrophobic nature of PFCL and SO, expelling any subretinal fluid at their interface.

When performing this technique, detach the irrigation line and replace it with a SO infusion cannula. An assistant may also hold the infusing SO cannula while it is being injected. Remove the PFCL passively through a soft-tip cannula at the optic nerve head. As the SO begins to enter the eye, removing the infusion fluid anterior to the PFCL bubble is helpful. Once this is done, you can place the cannula posteriorly over the optic nerve to remove PFCL as the SO is injected.

Tamponade Agent

Several factors influence the choice of tamponade agent in the treatment of GRT. A long-acting gas mixture of perfluoropropane (C3F8) is certainly convenient, as the gas bubble will resorb spontaneously. However, A.M. Al-Khairi, MD, and colleagues published a retrospective study of 115 patients, reporting a substantially higher rate of recurrent retinal detachment when gas was used (32 percent) than in eyes with silicone oil tamponade (13 percent).[3]

Nonetheless, a randomized controlled study of 47 eyes with comparable baseline characteristics showed no statistically significant differences in outcomes at 48 months postoperatively with either C3F8 or SO tamponade.[4] Retinal attachment was accomplished in 86 percent of the C3F8 group, in 89 percent (eight eyes) of the retained-SO group and in 94 percent (15 eyes) of those with SO removed.

SO is undoubtedly helpful in the presence of PVR, inferior GRT or when a patient is unable to comply with postoperative positioning requirements. Studies investigating the management of GRT RRD with silicone oil concluded that the primary retinal attachment rate was between 74 percent and 96 percent.[5-7]

Nurten Unlu, MD, and colleagues removed the SO in all patients and, after a mean follow-up of eight months, reported a reattachment rate of 81 percent.[6] Our preference is to use SO unless the tear is localized to the superior retina and PVR is absent, in which case, we would use C3F8 gas.

Scleral Buckle

The role of adjuvant encircling scleral buckling (SB) to pars plana vitrectomy (PPV) in GRT RRD is controversial among retinal surgeons. SB provides support to the vitreous base and thus relieves vitreoretinal tractional forces responsible for reopening or extension of the retinal break.[8]

SB, however, can result in fish-mouthing and redundant retinal folds, enabling posterior tear slippage. In our experience, we do not routinely add a scleral buckle and, in cases of an inferior GRT, we feel that heavy silicone oil (Densiron 68) with upright supine positioning achieves good results.

Proliferative Vitreoretinopathy

The rate of PVR in GRT with RRD is higher, in part, due to the extensive zone of exposed retinal pigment epithelium. Its incidence in the

(Continued on page 45)

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

Reporting Self-Identified Overpayments

What the 60-day rule for Medicare overpayments really means.

The government has a new weapon in its enforcement arsenal. In February 2016, the Department of Health and Human Services (HHS) published its final rule for reporting and returning Medicare overpayments.[1] This final rule implements section 6402(a) of the Affordable Care Act (ACA) and mandates that Medicare Part A and B providers and suppliers report and return overpayments within 60 days after they are identified or face steep penalties. The final rule became effective March 14, 2016. Follow these steps to address Medicare overpayments and/or credit balances.

Rule Changed with ACA

Section 6402 of the ACA expanded the Social Security Act by adding subsection 1128J(d). It requires a person who receives an overpayment to report and return the overpayment to the entity that issued it with an explanation of the overpayment.[2] The rule also sets a schedule for reporting and returning overpayments by the later of:

> *(A) the date which is 60 days after the date on which the overpayment was identified; or*
>
> *(B) the date any corresponding cost report is due, if applicable.*[2]

Enforcement of the 60-day rule comes under the federal False Claims Act (FCA) (31 U.S.C. §3729(b)(3)):

> *3) Enforcement—Any overpayment retained by a person after the deadline for reporting and returning the overpayment under paragraph (2) is an obligation (as defined in section 3729(b)(3) of title 31, United States Code) for purposes of section 3729 of such title.*
>
> *(4) Definitions—In this subsection:*
>
> *(A) Knowing and Knowingly—The terms "knowing" and "knowingly" have the meaning given those terms in section 3729(b) of Title 31, United States Code.*
>
> *(B) Overpayment—The term "overpayment" means any funds that a person receives or retains under Title XVIII or XIX to which the person, after applicable reconciliation, is not entitled under such title.*[2]

The FCA incorporates substantial penalties. The Civil Monetary Penalties Inflation Adjustment, effective August 1, 2016,[3] sets penalties at $10,781 to $21,563 for each false claim, plus up to three times the amount claimed. The FCA defines "knowledge" as: actual knowledge; deliberate ignorance of the truth or falsity of the information; or reckless disregard of the truth or falsity of the information.[4]

Early Interpretations

Following passage of the ACA overpayment provision, significant debate surrounded the meaning of "...the date which is 60 days after the date on which the overpayment was identified," and in particular over the definition of "identified." In August 2015, the Court for the Southern District of New York in *U.S. ex rel. Kane v. Healthfirst Inc.* issued the first judicial opinion on the 60-day rule and found:

> *To define 'identified' such that the sixty-day clock begins ticking when a provider is put on notice of a potential overpayment, rather than the moment when an overpayment is conclusively ascertained, is compatible with the legislative history of the FCA and the FERA [Fraud Enforcement and Recovery Act of 2009] highlighted by the Government.*[5]

Accordingly, the court held that the date on which a potential overpayment was identified was enough to start the clock. The court also indicated that choosing not to investigate does not eliminate the urgency inherent in the 60-day rule. The court wrote that a provider "has identified an overpayment when the [entity] has determined, or should have determined through the exercise of reasonable diligence, that [it] has received an overpayment," and adds:

> *... reasonable diligence might require an investigation conducted in good faith and in a timely manner by qualified individuals in response to credible information of a potential overpayment. ... to require 'actual knowledge,' ... would permit organizations to 'easily avoid returning improperly received payments.'*[5]

Identifying the Overpayment

In *Kane*, the court held that the 60-day clock started the moment a provider is first put on notice of a potential overpayment. In the final rule, however, the Centers for Medicare and Medicaid Services (CMS) provides clarity and gives providers additional time to investigate a possible overpayment:

> *A person has identified an overpayment when the person has, or should have through the exercise of reasonable diligence, determined*

that the person has received an overpayment and quantified the amount of the overpayment. A person should have determined that the person received an overpayment and quantified the amount of the overpayment if the person fails to exercise reasonable diligence and the person in fact received an overpayment.[1]

In 2015 the government settled a case with Pediatric Services of America (PSA) for its alleged failure to disclose and return Medicare and Medicaid overpayments. PSA retained credit balances from government payers by absorbing them into their revenue. The Justice Department reported this was the first settlement under the FCA involving a health-care provider's failure to investigate credit balances to determine whether they resulted from overpayments, citing section 6402 of the ACA and the 60-day rule.[6]

Mere notification of a possible overpayment does not start the 60-day clock. In the final rule, CMS requires that any investigation of a potential overpayment be completed within six months from receipt of the credible information, absent extraordinary circumstances.

Depending on the overpayment issue, "reasonable diligence" may necessitate looking back in time. The final rule establishes a six-year look-back period. The six years starts on the date the initial overpayment was received.[1]

Going Forward

Providers can no longer maintain a relaxed attitude about potential overpayments. Skirting the issue is very dangerous. Consider a proactive approach to mitigate your risk by developing a compliance plan as the Office of Inspector General outlines in the "Compliance Program Guidance for Individual and Small Group Physician Practices."[7] RS

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(Continued from page 43)

literature varies from 9 to 62 percent.[1] To reduce PVR, we routinely inject 0.5 mg of preservative-free triamcinolone (40 mg/mL) into the vitreous cavity at the end of our surgery.

Interestingly, new medications on the horizon may eventually aid the treatment of PVR in patients undergoing GRT RRD repair. Reports have shown that resveratrol, for example, has suppressed the development of experimental PVR in rabbit eyes.[9] Cannabinoids acting at the cannabinoid 2 receptor (CB2R) could also be a potential therapy for PVR. In fact, results of a study using a CB2R agonist at early stages of PVR in mouse eyes showed diminished ocular inflammation and disease severity.[10]

Take-Home Point

The principles of successful management of GRT with RRD consists of a thorough vitrectomy, unfolding of the posterior retinal flap tear, complete removal of subretinal fluid, creation of a firm chorioretinal adhesion around GRT and adequate internal tamponade.

Meticulous subretinal fluid drainage using the extrusion cannula at the posterior edge of the GRT is paramount to the success of GRT management. Surgical approaches, such as using adjunctive SB and selecting the type of endotamponade agent, are often individualized based on the clinical scenario and surgeon preference. RS

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Making the Case for SOPs

Standard operating procedures can save time and effort for practices participating in clinical trials. ***By Dianne R. Himmelman, RN, BSN, CCRC, and Diane Weiss, RN, BSN***

For practices active in clinical trials, having policies on how to carry out and document the work a clinical trial involves can streamline operations and help ensure the trial sponsor is collecting valid data from the practice. This is where good Standard Operating Procedures, or SOPs, can have great value.

SOPs are not unique to clinical trials and research. In the military, the term "standing operating procedures" was first noted in the mid-20th century. Federal and state governments, large and small private businesses, universities and hospitals all use SOPs.

The purpose of site SOPs is to provide step-by-step instructions on how to complete a specific activity or task required for good practice. They are designed to ensure quality through standardization and increase efficiency, which in turn will improve performance and work quality. SOPs can also supplement training and provide a resource for new employees to self-answer their questions. Furthermore, following SOPs will help to ensure subject safety, regulatory compliance and data integrity.

SOPs and FDA Guidelines

Since the 1970s, the Food and Drug Administration (FDA) has regulated the conduct of clinical research trials. The Code of Federal Regulations (CFR) offers guidelines on how investigators should conduct clinical research. While they are guidelines, not specific rules or laws, the CRF guidelines are enforceable if the FDA finds that a clinical research site is not adhering to them. The most common and practical way to meet these guidelines is through the use of SOPs.

The International Council for Harmonisation defines SOPs as "detailed, written instructions to achieve uniformity of the performance of a specific function."

Creating SOPs can be daunting, often adding more work for staff already bogged down by paperwork. However, they give guidance to the clinical research staff on many specific research activities that can range from how to complete specific forms, to more complicated issues in regard to principal investigator (PI) oversight.

The SOPs Format

SOPs, which a partnering agency can also write, should follow a specific format that includes:

- Title/policy number/issue date/implementation date/revision date(s), necessary to provide organization of the policies.
- Scope, which covers the area the SOPs address and to whom the SOPs apply.
- Policy, which covers the goal of the SOPs.
- Procedure, which may include applicable attachments, provides the specific details to achieve the policy within its scope. Attachments can consist of examples, forms or logs for conducting the SOP.

Frequently, SOPs will also cite the CFR guideline or other regulatory authority.

SOPs must also be reviewed annually to ensure they comply with updated industry standards, regulatory guidelines and current site processes. This review, and any necessary modifications, can be quite time consuming.

One drawback of SOPs is that an FDA audit can cite noncompliance if the practice doesn't follow them as written. Conversely, the lack of SOPs may be more troublesome to the FDA than limited compliance to a specific one. Involving the clinical staff in writing SOPs may help reduce noncompliance by verifying they understand the procedures and that the procedures are valid in the real world.

Less Work on the Back End

While SOPs may demand more time and create more paperwork for your research staff on the front end, in the long-run their use can lead to less work on the back end, especially if your site experiences an audit by a sponsor, Institutional Review Board (IRB) or FDA.

Findings from an FDA audit can haunt a site for years because it puts into question the site's ability to perform quality work. Though at the time of new study submissions, IRBs request information about a site's five-year FDA audit history, sponsors can ask for the disclosure regardless of when it occurred.

At first glance SOPs appear to be one more layer of regulatory paperwork. However, when you consider their simple purpose—as written processes that enable a site to perform a task the same way each time—their importance is obvious. As with all good research, replication helps advance understanding.

Ms. Himmelman is a clinical research nurse at Retina Associates of Cleveland, Beachwood, Ohio. Ms. Weiss is clinical research coordinator and manager of clinical trials there.

By Richard Mark Kirkner »

Can Sirolimus Solve the Taper Puzzle?

SAKURA results point the way to successful tapering of steroids in noninfectious posterior uveitis.

One of the clinical challenges of treating noninfectious posterior uveitis with systemic corticosteroids is tapering patients without risk of flare ups, but two ongoing trials of intravitreal sirolimus have reported significant reduction of vitreous haze as patients were successfully tapered off their systemic corticosteroids, according to results of Phase III trials presented as posters at the Association for Research in Vision and Ophthalmology meeting.[1,2]

SAKURA—it stands for Sirolimus study Assessing double-masKed Uveitis tReAtment—is the largest clinical program to date evaluating patients with noninfectious posterior uveitis. The program comprises two multinational, randomized, double-masked Phase III trials that are evaluating intravitreal sirolimus 440 µg and 880 µg vs. 44 µg as the comparator. The ARVO reports involved the intent-to-treat (ITT) population comparing the 44 µg and 440 µg treatment arms.

How Sirolimus Works

Sirolimus has been used systemically as an anti-rejection agent in patients who have had kidney transplants. Raj K. Maturi, MD, of Midwest Eye Institute in Indianapolis, one of the SAKURA investigators, explains how sirolimus works in noninfectious posterior uveitis. "Essentially it has multiple mechanisms of action where it uses this unique system called TOR, or target of rapamycin, and it inhibits the mammalian target of rapamycin, or mTOR, which is a very central mechanism for inhibition of leukocyte activation and certain processes affecting regulated T cells, as well as decreasing vascular endothelial growth factor to reduce edema in uveitis," he says.

Quotable

"A uveitis trial is very difficult to run because patients are so different and the disease is so heterogeneous."

— Raj K. Maturi, MD

Dr. Maturi also explains why clinical trials of uveitis are lacking. "A uveitis trial is very difficult to run because patients are so different and the disease is so heterogeneous."

The SAKURA studies include 592 patients—347 in Study 1 and 245 in Study 2. Subjects from both studies comprised the ITT population with 208 in each the sirolimus 440 µg and 44 µg active control groups, with 46 from the 440 µg and 32 from the active controls designated for the intent-to-taper group. The studies define tapering success as achieving an overall prednisone-equivalent dose of ≤5 mg/day at month five without rescue therapy.

Tapering success with vitreous haze reduction was higher in the 440-µg vs. the active controls (43.5 percent vs. 28.1 percent), although the small sample size precludes a declaration of any statistically significant difference (p=0.1676).

The Nature of the Taper

"There's good tapering success with the drug," Dr. Maturi says. "If you look at the combined data of the two trials, they've clearly reached their primary endpoints in getting patients to no inflammation. It also shows that a higher proportion of patients end up being successfully tapered off of oral steroids."

While the numbers are small, the take-home for Dr. Maturi was the nature of the tapering that was not reported in the data. "On a majority of patients we were able to literally taper their oral steroids quite successfully over just a few weeks after beginning sirolimus," he says. "We didn't have any patients we had to go back and add steroids to either orally or systemically because their drug did not work."

Commercialization on Track

Santen is on track with its commercialization program for sirolimus, which it has labeled DE-109 in its Food and Drug Administration filing. Santen filed the New Drug Application in February and received word of its acceptance in April. At the company's annual meeting in May, Chief Scientific Officer Naveed Shams, MD, PhD, told shareholders launch is expected in the first half of next year, pending approval.

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FA Insert Delivers At 12 Months

Top-line results through 12 months show sustained effect of three-year insert for noninfectious posterior uveitis. ***By Richard Mark Kirkner***

Recurrent inflammatory flare-ups characterize the chronic nature of noninfectious posterior uveitis. Repeated courses of corticosteroids have been the therapy of choice, but they are associated with well-documented ocular side effects, namely increased intraocular pressure and cataract formation.

The need for a treatment that provides effective and continuous control of the disease with an acceptable safety profile has set off a scramble to develop longer-term drug-treatment platforms that include surgical implants and injectable inserts. At the Association for Research in Vision and Ophthalmology last month, investigators reported successful top-line 12-month data from a three-year fluocinolone acetonide (FA) insert (Durasert, pSivida Corporation) for the treatment of chronic noninfectious posterior uveitis.[1]

The lower doses of FA that the insert delivers may avert the problems of prolonged oral therapy and repeated steroid injections for recurrent noninfectious uveitis, says Dario Paggiarino, MD, vice president and chief medical officer of pSivida.

Twelve-month data from the first of two three-year, Phase III trials showed a reduction of recurrence and modest rises in intraocular pressure. Recurrence rates were 27.6 percent for the treatment group vs. 85.7 percent for sham in the intention to treat population ($p<0.001$). The sham group was also more likely to use adjunctive therapy at 12 months; 61.9 percent required intra- or periocular steroids vs. 6.9 percent of the insert group. The trial involves 129 subjects randomized to the insert and sham.

Quotable

"The 12-month data showed the insert continued the reduction in disease recurrence previously reported with the six-month data"

— Dario Paggiarino, MD

Here, Dr. Paggiarino answers key questions about the insert.

Q How does the insert work?

A The insert is administered through a single intravitreal injection in the office and delivers micro-doses ranging from 0.13 to 0.15 µg of FA daily over three years, which is significantly longer than currently approved intravitreally injected treatments. This modality may be ideal to address the chronic and recurrent nature of the condition. Avoiding disease flares is important because they can cause irreversible damage to the neuroretina.

Q What's the key take-home from the first Phase III trial?

A The 12-month data showed the insert continued the reduction in disease recurrence previously reported with the six-month data. From a safety standpoint, we did observe the typical steroid effect, but because of micro-dosing the increase in IOP on average is modest compared to sham—1.3 mmHg vs. 0.2 mmHg in the sham group. Overall the effect on IOP as a result of a single insert injection seems to be modest and also fairly predictable, stable and manageable over 12 months. The percentages of patients who required IOP-lowering therapy at 12 months were almost identical: 26.4 percent for the insert group and 26.2 percent for sham.

With regards to cataract, of the phakic patients at study entry 33.3 percent in the treatment group needed surgery vs. 4.8 percent in the sham group. However, about half of the study population was already pseudophakic at entry.

Q What's the big question that the three-year results should answer?

A The 12-month data is very encouraging, and the question becomes what is the long-term effect of micro-dosing of FA in terms of maintaining patients recurrence-free, limiting the number of recurrences, and, of course, the long-term safety profile.

Q What's next?

A The second of the two Phase III studies is expected to read out this month. Pending its findings, a New Drug Application in the United States should be filed by the end of the year. Also, this insert technology has other potential applications beyond noninfectious posterior uveitis and even beyond ophthalmology. RS

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Professional Opportunities

RETINA SPECIALIST - Eastern Pennsylvania

Great opportunity for a Board Eligible/Board Certified Ophthalmologist with retina fellowship training looking to join a collegial group in an established and growing Ophthalmology practice in eastern Pennsylvania. Lehigh Valley Health Network (LVHN) has an employed Ophthalmology group which is currently comprised of two Ophthalmologists and an Optometrist based in Allentown, Pennsylvania. This practice is looking to expand office locations and specialty services. Our new Retina Specialist will provide ROP Screening for the NICU, perform procedures, see patients in clinic and share in call coverage for emergencies. We are offering a comprehensive compensation package including attractive salary, CME time and top-tier benefits.

We are located in the beautiful Lehigh Valley, a fast growing region in eastern Pennsylvania comprised of three mid-sized cites surrounded by suburban neighborhoods with over 700,000 residents. The area has a moderate cost of living, outstanding public and private school systems, ten colleges and universities, and an abundance of cultural and recreational offerings including two symphonies, summer music festivals, an art museum, and minor league sport teams. Just a 60 minute drive north of Philadelphia and 90 minute drive west of New York City.

Lehigh Valley Health Network (LVHN) is a nonprofit community hospital system with over 1,300 beds across 5 full service hospital campuses including a Level 1 Trauma Center, with an employed multispecialty physician group or 160 practices, and 20 fully accredited, free standing residency and fellowship programs. U.S. News & World Report has ranked LVHN among America's Top Hospitals for 21 consecutive years and currently has two of our hospital campuses ranked in the top 20 hospitals in the state of Pennsylvania.

Interested Ophthalmologists should send a CV to
Mark.Payson@LVHN.org
or call 484-862-3205 for more information.
Visit our website at www.LVHN.org

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EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME. The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.7 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA.

Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

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

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

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 Postmarketing Experience. The following adverse reactions have been identified during postapproval use of EYLEA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity including rash, pruritus, and urticaria as well as isolated cases of severe anaphylactic/anaphylactoid reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
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Issue Date: June 2016
Initial U.S. Approval: 2011
June 2016

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

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