

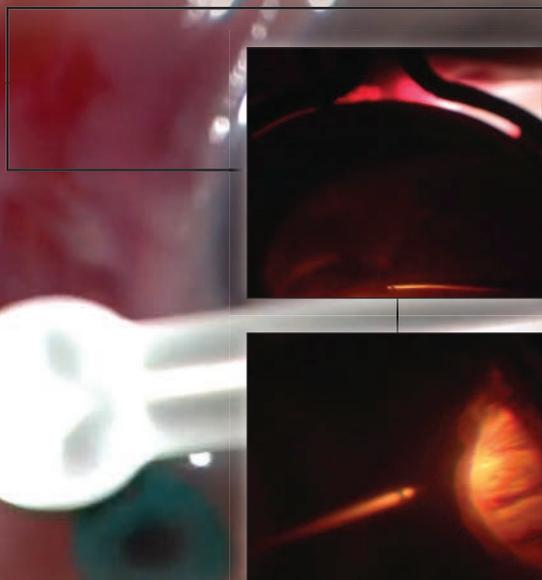
RETINA SPECIALIST

VOL. 5, NO. 5 • SEPTEMBER/OCTOBER 2019

Imaging Forum: What's the cause of painless vision loss, panuveitis? Page 10

Page 14 Uveitis Forum: Avoid these pitfalls when ordering labs for uveitis

Focus on Surgery



PERIPHERAL VITRECTOMY WITHOUT AN ASSISTANT

How scleral depression-transillumination can enhance our view of the peripheral retina. Page 20

With Online Video

Rethinking steroid drops after vitreoretinal surgery – page 24

Online Video

Pearls for RD repair after ruptured globe – page 19

Also Inside

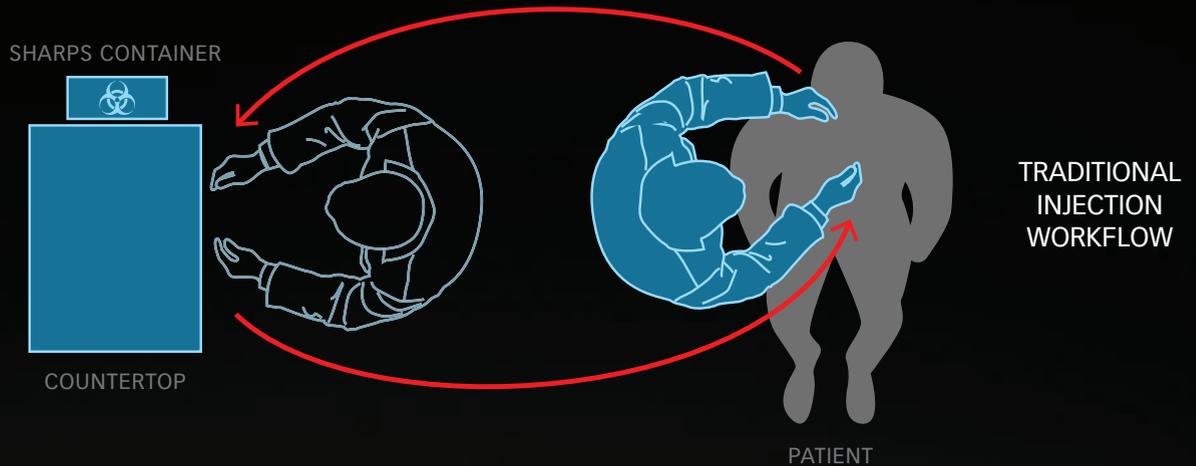
Strategies for improving safety for office procedures – page 28

How ultra-widefield imaging is changing our view of DR – page 32

Report from ASRS 2019: Downside of finger flicks, upside of abicipar changes – page 36

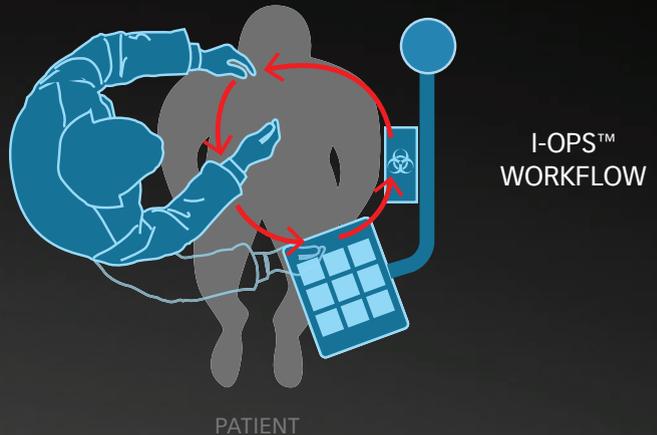
Retina CEO: Secure your tech and stay compliant – page 40

Once you've used I-OPS™, there's no turning back.



The ergonomically designed I-OPS™ Instrument Delivery System.

Streamline injections without straining your back.



I-OPS ergonomically optimizes instrument delivery so you can perform intraocular injections much more efficiently and comfortably. Nine customizable, clearly labeled inserts securely hold and present supplies for quick and easy one-handed retrieval – and there's no twisting or turning to strain your back or slow your workflow.

INNOVATION WITHIN EASY REACH.
Contact us about a risk-free in-office demo today.

800.735.0357
iops.reliance-medical.com

© 2019 Haag-Streit USA. All Rights Reserved.



RELIANCE
INTERNATIONAL



11 Campus Blvd., Suite 100
Newtown Square, PA 19073
Telephone (610) 492-1000
Fax (610) 492-1039
Editorial inquiries (610) 492-1000
Advertising inquiries (610) 492-1011
E-mail retinaspecialist@jobson.com

EDITORIAL STAFF

EDITOR-IN-CHIEF

Walter Bethke
wbethke@jobson.com

CHIEF MEDICAL EDITOR

Charles C. Wykoff, MD, PhD
ccwmd@houstonretina.com

EDITOR

Richard Mark Kirkner
rkirkner@jobson.com

ART DIRECTOR

Jared Araujo
jaraujo@jhihealth.com

SENIOR GRAPHIC DESIGNER

Matt Egger
megger@jhihealth.com

GRAPHIC DESIGNER

Ashley Schmuoder
aschmuoder@jobson.com

AD PRODUCTION MANAGER

Scott Tobin
stobin@jhihealth.com

EDITORIAL BOARD

Ashkan M. Abbey, MD, Dallas
David R.P. Almeida, MD, MBA, PhD, Erie, Pa.
Kevin Corcoran, COE, CPC, San Bernardino, Calif.
Emmett T. Cunningham Jr., MD, PhD, San Francisco
Lisa Olmos de Koo, MD, MBA, Seattle
Paul Hahn, MD, PhD, Teaneck, N.J.
Jason Hsu, MD, Philadelphia
Efrem D. Mandelcorn, MD, FRCS, Toronto
Jonathan L. Prenner, MD, Edison, N.J.
Kari Rasumussen, Park City, Utah
Carl D. Regillo, MD, FACS, Philadelphia
Philip J. Rosenfeld, MD, PhD, Miami
Akshay S. Thomas, MD, MS, Nashville, Tenn.

EDITORIAL CONTRIBUTORS

Ellen R. Adams, MBA, Boston
Elizabeth Atchison, MD, Sioux Falls, S.D.
Daniel M. Berinstein, MD, Chevy Chase, Md.
Kevin Broderick, MD, Chevy Chase, Md.
Brian K. Do, MD, Chevy Chase, Md.,
Sana Idrees, MD, Rochester, N.Y.
Thomas L. Jenkins, MD, Philadelphia
Talia R. Kaden, MD, Garden City, N.Y.
Ajay E. Kuriyan, MD, Rochester, N.Y.
Joshua D. Levinson, MD, Chevy Chase, Md.
Yasha Modi, MD, New York
John Pollack, MD, Joliet, Ill.
Rajeev Ramchandran, MD, MBA, Rochester, N.Y.
Bozho Todorich, MD, PhD, Camp Hill, Pa.



Family of Five

Management of exudative retinal diseases was forever changed with the advent of anti-VEGF pharmacotherapies, a revolution that continues to unfold with brolicizumab (Novartis) awaiting Food and Drug Administration approval and at least seven additional anti-VEGF drugs progressing through human trials. But, in light of the recent Phase II trial investigating vascular endothelial growth factor-C and -D blockade, we should clarify that these drugs primarily target vascular endothelial growth factor A.

Recall that the VEGF family comprises five cytokine members. VEGF-A, the first to be cloned 30 years ago in 1989 by Napoleone Ferrara, appears to be predominantly responsible for the pathologic angiogenesis and vascular leakage in retinal diseases. But, other members of the family have also been implicated in the pathogenesis of retinal diseases.

Unfortunately, validation of an alternative target that delivers additive benefit beyond anti-VEGF-A monotherapy has proven remarkably challenging. While notorious failures such as anti-PDGF drugs litter our past, I believe our future is brighter.

Multiple active clinical trials hold tremendous promise that we may break through the VEGF-A monotherapy glass ceiling. Positive results with combined VEGF-A and angiopoietin-2 blockade in the BOULEVARD Phase II trial drove the bispecific crossmab faricimab

(Roche/Genentech) into multiple ongoing Phase III trials, with read-outs anticipated within two years.

Most recently, OPT-302 (Opthea) achieved its primary endpoint of superiority in a 366-patient Phase IIb randomized trial comparing ranibizumab (Lucentis, Roche/Genentech) monotherapy to combination therapy of ranibizumab and OPT-302. OPT-302 is an engineered trap molecule based on the soluble, extracellular portion of VEGF receptor 3 designed to inhibit the activity of VEGF-C and -D.

Among treatment-naïve patients with neovascular age-related macular degeneration, combination dosing achieved 14.2 letters gained at 24 weeks, or a statistically significant 3.4 more letters compared with ranibizumab monotherapy, while secondary endpoints, including anatomic outcomes, supported the primary outcome of superiority. (For more on OPT-302, see *Clinical Trial Closeup*, "Closing the escape route of anti-VEGF-A agents," page 45.)

Ongoing Phase III trials with faricimab and anticipated registration trials with OPT-302 bring a fresh sense of hope and opportunity to the retina community. 

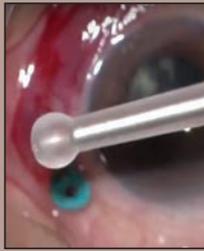
A PUBLICATION BY RETINA

RETINA SPECIALIST

SEPTEMBER/OCTOBER 2019 • VOL. 5, NO. 5

FEATURES

Focus On Surgery



20 Peripheral vitrectomy without an assistant

 Scleral depression-transillumination to enhance peripheral retina view.

By Bozho Todorich, MD, PhD



24 Rethinking steroid drops after vitreoretinal surgery

Why do we use postop drops the way we do? Case for subconjunctival triamcinolone.

By Elizabeth Atchison, MD, and John Pollack, MD

ALSO INSIDE:

28 Strategies for improving safety for office procedures

Patient safety challenges in the retina practice and steps to eliminate procedure errors.

By Kevin Broderick, MD,
Joshua D. Levinson, MD, and
Daniel M Berinstein, MD

36 Report from ASRS 2019: Downside of finger flicks, upside of abicipar changes

A look at five presentations that give new insights into nAMD.

By Ashkan M. Abbey, MD

32 How UWF imaging is changing our view of DR

The state of the science of ultra-widefield imaging for observing peripheral changes.

By Sana Idrees, MD,
Rajeev S. Ramchandran, MD, MBA,
and Ajay E. Kuriyan, MD, MS

DEPARTMENTS

3 Editor's Page

Family of Five

By Charles C. Wykoff, MD, PhD

7 News

Intravitreal injections and costs;

What diabetes patients read online

10 Imaging Forum

What's cause of painless vision loss?

Edited by Jason Hsu, MD

14 Uveitis Forum

Pitfalls to avoid when ordering labs

Edited by Ashkay Thomas, MD

19 Surgical Pearl Video

 Pearls for RD repair after

[Online Video](#) a ruptured globe

Edited by Paul Hahn, MD

40 Retina CEO

Secure your tech and stay compliant

Edited by Kari Rasmussen

42 Coding Commentary

Step therapy: Where do we stand?

By Ellen R. Adams, MBA

44 Social Media Specialist

Twitter as a 'microblog'

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

45 Clinical Trial Closeup

Closing escape route of anti-VEGF-A

Edited by Emmett T. Cunningham Jr., MD, PhD

0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED¹

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

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a sterile glass prefilled syringe.¹



INDICATIONS

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

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

IMPORTANT SAFETY INFORMATION

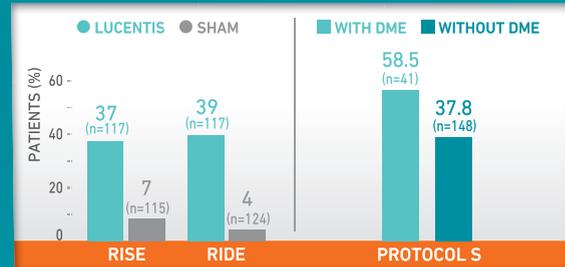
CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

≥2-STEP IMPROVEMENTS AT 2 YEARS^{1*}



≥3-STEP IMPROVEMENTS AT 2 YEARS¹:

RISE AND RIDE

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

PROTOCOL S

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

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

ADVERSE EVENTS

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

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

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

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

DME, diabetic macular edema.

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

Genentech
A Member of the Roche Group

© 2018 Genentech USA, Inc.
1 DNA Way, South San Francisco, CA 94080-4990
All rights reserved. LUC/120517/0094(1) 11/18

LUCENTIS
RANIBIZUMAB INJECTION

LUCENTIS[®]

RANIBIZUMAB INJECTION

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

1 INDICATIONS AND USAGE

LUCENTIS is indicated for the treatment of patients with:

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

4 CONTRAINDICATIONS

4.1 Ocular or Periorcular Infections

LUCENTIS is contraindicated in patients with ocular or periorcular infections.

4.2 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

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

5.2 Increases in Intraocular Pressure

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

5.3 Thromboembolic Events

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

Neovascular (Wet) Age-Related Macular Degeneration

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

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

Macular Edema Following Retinal Vein Occlusion

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

Diabetic Macular Edema and Diabetic Retinopathy

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

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

5.4 Fatal Events in Patients with DME and DR at Baseline

Diabetic Macular Edema and Diabetic Retinopathy

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

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

6 ADVERSE REACTIONS

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

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

6.1 Injection Procedure

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

6.2 Clinical Studies Experience

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

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

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

Ocular Reactions

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

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

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

Non-Ocular Reactions

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

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

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

8.3 Females and Males of Reproductive Potential

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

LUCENTIS[®] [ranibizumab injection]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017
LUCENTIS[®] is a registered trademark of Genentech, Inc.
©2017 Genentech, Inc.

Intravitreal injections fill up your day, but maybe not your balance sheet

Appointments for intravitreal injections of anti-VEGF drugs fill up your schedules and make you rush through your day, but a single-center study presented at the American Society of Retina Specialists 37th annual scientific meeting shows they may be doing something else for your practice: losing money.¹

Christina Y. Weng, MD, MBA, an associate professor at Baylor College of Medicine, Cullen Eye Institute in Houston, presented results from a single-center observational cost analysis using accounting principles that showed her institution is losing an average of \$23.34 on each procedure reimbursed by Medicare. “The main take-home point is that the intravitreal injection procedure (CPT code 67028), one of the most commonly coded procedures in the United States, may be undervalued by payers,” Dr. Weng says in written comments to *Retina Specialist*.

The study used activity-based costing, an accounting method that allocates a cost to each component

of a process on a map. The total activity-based cost, not including the cost of the drug, was \$127.74; the Medicare reimbursement was \$104.40.

The median total time spent on an intravitreal injection in the study is 32 minutes, 58 seconds, and almost half of that was devoted to electronic health record documentation. Of that, about 12 minutes consisted of the retina specialist’s time, and more than half of that was spent on EHR rather than patient interaction. Other components of the process include greeting the patient and performing the injection itself. The EHR demands are consistent with other reports in the medical literature, Dr. Weng notes.

The cost estimate itself is “quite conservative,” Dr. Weng points out. It doesn’t account for sunken costs, such as the non-disposable speculum, nor does it account for variations in the injection technique that may be more costly. Also, because of its single-center nature, the findings are limited.

But there are lessons individual

practices can take from this study to evaluate their own costs of performing intravitreal injections, Dr. Weng says. “The neat thing about our study is that it does more than simply estimate resource consumption; it offers a generalizable approach that may allow us to more accurately quantify the costs of what we do,” she says.

That approach is to use activity-based costing (ABC), an accounting method with origins in manufacturing. “Essentially,” Dr. Weng says, “any procedure that is conducted in a practice can be analyzed using ABC by building a process map and applying internal accounting records to assign costs to the direct materials, direct labor and overhead consumed in performing that particular procedure.”

Dr. Weng disclosed financial relationships with Alcon, Allergan and Alimera Sciences.

REFERENCE

1. Weng CY. Process mapping and activity based costing of the intravitreal injection procedure. Abstract presented at the 37th annual Scientific Meeting of the American Society of Retina Specialists; July 28, 2019; Chicago, IL.

IN BRIEF

Novartis has formally launched TALON, a Phase IIIb clinical trial in neovascular age-related macular degeneration comparing brodalumab 6 mg and aflibercept 2 mg (Eyelea, Regeneron). The trial will enroll almost 700 patients. Novartis anticipates launching brodalumab later in the year.

The **American Medical Association’s CPT Editorial Panel** has accepted a new category 1 CPT code for automated point-of-care retinal imaging, clearing the way for reimbursement of an examination with the **IDx-DR**, an artificial-intelligence system that detects diabetic

retinopathy. The new CPT code for automated point-of-care retinal imaging goes into effect in January 2021.

The Food and Drug Administration has accepted **Allergan’s** Biologics License Application for abicipar pegol, a DARPin therapy for nAMD. Allergan expects the FDA to take action on the BLA in mid-2020.

A study in *JAMA Ophthalmology* reported that Luxturna (voretigene neparvovec-rzyl), **Spark Therapeutics’** gene therapy for RPE65-mediated inherited retinal disease that lists at \$425,000 per eye, is cost effective compared with standard care. Luxturna was associated with lower total costs (\$2.2 million vs. \$2.8 million) and higher quality-adjusted life-years (18.1 vs. 8.6).

What diabetes patients read online may not be helping anybody

Online information about diabetes and diabetic retinopathy is readily available and plentiful, but may not necessarily be accessible, applicable or practical.

Researchers at Bascom Palmer Eye Institute at the University of Miami reported in *JAMA Ophthalmology* that online information about diabetic retinopathy has two primary flaws: Not only is it “generally of low quality,” but it is also presented at a reading level beyond the comprehension of the typical user.¹ The report consisted of a cross-sectional study of 11 medical sites with information on DR.

“There appears to be a gap that needs to be addressed to make online resources both readily understandable by the layperson and clinically accurate,” corresponding author Jaynath Sridhar, MD, tells *Retina Specialist*. The average reading level for the studied websites was 11th grade, but prior studies have demonstrated that a third-grade level is appropriate for diabetic education because of the socioeconomic and educational barriers affecting many patients with diabetes.

“Too often, websites are either too basic and incorrect, or more accurate but too complex in their language and word choice,” Dr. Sridhar says.

Among the websites evaluated were the American Academy of Ophthalmology, All About Vision, American Optometric Association, American Society of Retina Specialists, National Eye Institute, EyeWiki, Mayo Clinic, WebMD and Wikipedia. The highest ranking was Wiki-

Quotable

“If these resources are not understandable or worse, inaccurate, then this may increase patient confusion of their condition and decrease commitment to strict follow-up and treatment. On the other hand, good online educational resources could play a huge role in combating this public health problem.”

— Jaynath Sridhar, MD

pedia, with a rating of 76.67 percent.

“In today’s digital age, patients will inevitably utilize online resources to try and educate themselves,” Dr. Sridhar says. “If these resources are not understandable or worse, inaccurate, then this may increase patient confusion of their condition and decrease commitment to strict follow-up and treatment. On the other hand, good online educational resources could play a huge role in combating this public health problem.”

Dr. Sridhar is a consultant for Alcon, Alimera and Thrombogenics.

REFERENCE

1. Kloosterboer A, Yannuzzi NA, Patel NA, Kuriyan AE, Sridhar J. Assessment of the quality, content, and readability of freely available online information for patients regarding diabetic retinopathy. *JAMA Ophthalmol*. 2019 Aug. 22. doi:10.1001/jamaophthalmol.2019.3116 [Epub ahead of print]

RETINA SPECIALIST

BUSINESS OFFICES

11 CAMPUS BOULEVARD, SUITE 100
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF

PUBLISHER

JAMES HENNE

(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER

MICHELE BARRETT

(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER

MICHAEL HOSTER

(610) 492-1028 MHOSTER@JOBSON.COM

CLASSIFIED ADVERTISING

(888)-498-1460

VICE PRESIDENT OF OPERATIONS

CASEY FOSTER

(610) 492-1007 CFOSTER@JOBSON.COM

PRODUCTION MANAGER

SCOTT TOBIN

(610) 492-1011 STOBIN@JOBSON.COM

SUBSCRIPTIONS

US ONE YEAR: \$63.00

CANADIAN ONE YEAR: \$99.00

FOREIGN ONE YEAR: \$158.00

SUBSCRIPTIONS E-MAIL:

RETINASPECIALIST@CAMBEYWEST.COM

CIRCULATION

RETINA SPECIALIST

PO BOX 397

CONGERS, NY 10920-0397

CIRCULATION CUSTOMER SERVICE

PHONE: (877) 529-1746 (U.S.)

OR (845) 267-3065 (OUTSIDE U.S.)

SENIOR CIRCULATION MANAGER

HAMILTON MAHER

(212) 219-7870 hmaher@jhihealth.com

CEO, INFORMATION GROUP SERVICES

MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS

JEFF LEVITZ

VICE PRESIDENT, HUMAN RESOURCES

TAMMY GARCIA

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION

MONICA TETTAMANZI

SENIOR CORPORATE PRODUCTION DIRECTOR

JOHN ANTHONY CAGGIANO

VICE PRESIDENT, CIRCULATION

EMELDA BAREA



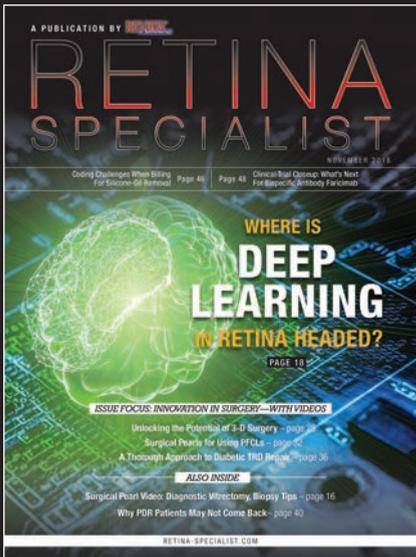
Jobson Medical Information LLC,

395 Hudson Street, 3rd Floor, New York, NY 10014

A PUBLICATION BY **REVIEW**
of Ophthalmology

RETINA SPECIALIST

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



Starting January 2019
Retina Specialist will
appear bimonthly.

Watch for issues in:

» **JANUARY**

» **JULY**

» **MARCH**

» **SEPTEMBER**

» **MAY**

» **NOVEMBER**

For inquiries contact

RETINASPECIALIST@JOBSON.COM

Advertising opportunities

JIM HENNE • PUBLISHER • 610-492-1017 • JHENNE@JOBSON.COM

MICHELE BARRETT • 215-519-1414 • MBARRETT@JOBSON.COM

MICHAEL HOSTER • 610-492-1028 • MHOSTER@JOBSON.COM

www.retina-specialist.com

What's the cause of painless vision loss?

Multimodal imaging played a valuable role in identifying primary vitreoretinal lymphoma in this patient with Alzheimer's.

By **Thomas L. Jenkins, MD,** and
Jason Hsu, MD



Department Editor
Jason Hsu, MD

A 75-year-old Caucasian woman presented with three days of symptomatic painless vision loss in the left eye. Her medical history included Alzheimer's dementia, and her ocular history was unremarkable with a remote, uncomplicated cataract extraction. On review of systems, she denied fevers, rashes, shortness of breath or other systemic symptoms.

Workup and imaging findings

The patient appeared generally healthy, and her vital signs were within normal limits. On ocular examination, visual acuity with correction was 20/25 OD and counting fingers OS. Intraocular pressures were 37 mmHg OD and 44 mmHg OS. Anterior segment examination revealed 2+ cell OD and 3+ cell OS without granulomatous keratic precipitates or hypopyon. Posterior segment examination of the right eye showed 1+ vitreous cell with superotemporal multifocal subretinal yellow-white material and focal nasal vascular sheathing (*Figure 1*). Posterior evalua-

tion of the left eye showed 2+ vitreous cell with a large collection of subretinal white material superiorly and scattered areas of chorioretinal atrophy.

Fluorescein angiography (*Figure 2*) of both eyes revealed multifocal areas of punctate hyperfluorescence with late staining. Optical coherence tomography of the right eye was unremarkable. In the left eye, OCT demonstrated attenuation of the ellipsoid zone and small multifocal sub-retinal pigment epithelium deposits (*Figure 3, page 12*).

The differential diagnosis of this patient with bilateral posterior uveitis with retinal or subretinal whitening included infectious, inflammatory and neoplastic etiologies. Infectious causes included bacterial (e.g., tuberculosis, syphilis, Lyme disease), viral (e.g., herpetic necrotizing retinitis), and fungal and protozoan organisms. Inflammatory diseases like sarcoidosis were considered but thought to be less likely. Neoplastic causes such as primary vitreoretinal lymphoma (PVRL), secondary spread of systemic lymphoma,

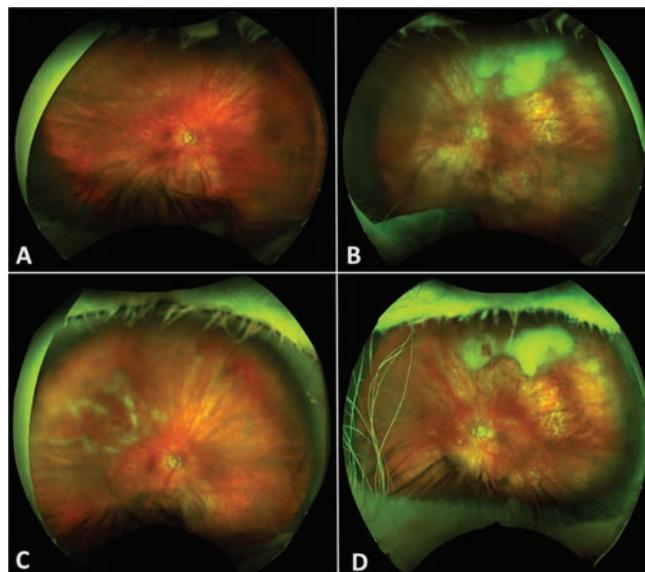


Figure 1. Widefield imaging at initial presentation of the right eye (A) shows superotemporal, poorly defined yellow-white subretinal material. Left-eye imaging (B) shows superotemporal elevated white infiltrates and peripheral chorioretinal atrophy. Six weeks later, the right eye (C) shows significant progression of subretinal yellow-white infiltrates now with associated intraretinal hemorrhages, and the left eye (D) shows consolidation of superotemporal subretinal material with new retinal hemorrhages.

Bios

Drs. Jenkins and Hsu are with Mid-Atlantic Retina/Retina Service, Wills Eye Hospital, Philadelphia.

DISCLOSURES: Drs. Jenkins and Hsu have no relevant financial relationships to disclose.

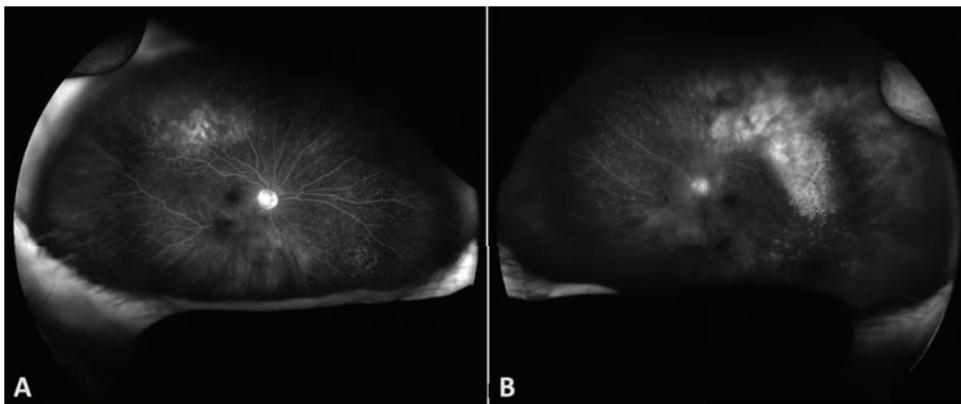


Figure 2. Widefield fluorescein angiogram of the right (A) and left (B) eyes show irregular hyper- and hypofluorescence with late staining in both eyes corresponding to elevated yellow-white infiltrates seen clinically. In the left eye, leakage appears from the superotemporal retinal vasculature.

and leukemic infiltration were strongly considered.

Work-up, diagnosis and treatment

This patient's anterior uveitis was initially treated with prednisolone acetate 1% every two hours in both eyes. IOP-lowering drops were initiated for ocular hypertension. An anterior chamber paracentesis for the ocular patient care report (PCR) was negative for varicella zoster virus, herpes simplex virus-1 and -2, cytomegalovirus and toxoplasmosis. Blood work, including Lyme antibody, syphilis serologies, quantiFERON-tuberculosis gold, angiotensin converting enzyme, complete blood count, and a complete metabolic panel returned normal.

One month after her initial presentation, the patient's IOPs had improved to 14 mmHg OD and 16 mmHg OS, and her visual acuity remained unchanged. Fundoscopic examination revealed progression of the fluffy white infiltrates with associated retinal hemorrhages superotemporally in the right eye with consolidated-appearing fluffy white subretinal material in the left eye.

Given the progression of disease and negative workup, a diagnostic and therapeutic pars plana vitrectomy with subretinal aspiration biopsy was undertaken in the left eye. Histopathologic examination of the vitreous specimen showed rare atypical B-cells in a background of chronic

granulomatous vitritis. In contrast, subretinal needle biopsy showed high-grade B-cell lymphoma compatible with diffuse large B-cell lymphoma of primary vitreoretinal or primary central nervous system origin.

Further PCR testing of the subretinal material demonstrated *MYD88 L265P* mutation, supporting a diagnosis of vitreoretinal lymphoma. MRI of the brain and orbit revealed a 1-x-1.7-cm right frontal and 8-x-7-mm right occipital cortical-based masses with extensive vasogenic edema (Figure 4, page 13).

Presentation of disease

Primary vitreoretinal lymphoma (PVRL) is an ocular subset of primary CNS lymphoma (PCNSL) that initially presents in the eyes. Roughly one third of patients with PCNSL will have manifestation of VRL at the time of CNS diagnosis, while 48 to 92 percent of patients with PVRL will go on to develop CNS manifestations over a mean follow-up of eight to 29 months.¹

Both diseases are considered rare extranodal, non-Hodgkin's lymphomas that are generally diagnosed as a high-grade, diffuse, large B-cell lymphoma. Most cases occur in patients age 50 to 70 years. Immunocompromised status is a major risk factor for PCNSL, especially in young populations, with a steep rise in reported cases from the 1970s to 1990s due in part

Primary vitreoretinal lymphoma (PVRL) is an ocular subset of primary CNS lymphoma (PCNSL) that initially presents in the eyes. Immunocompromised status is a major risk factor for PCNSL.

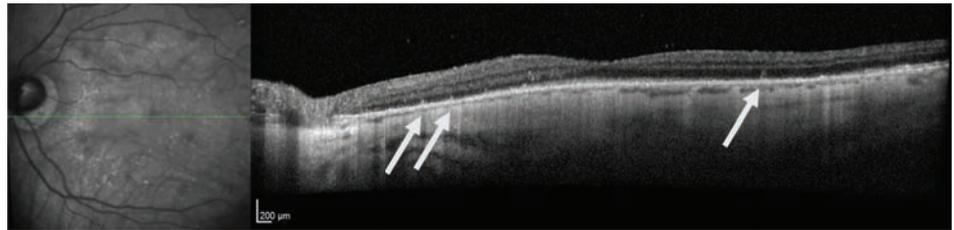


Figure 3. Enhanced-depth optical coherence tomography of the left eye shows overlying vitreous cells, ellipsoid layer attenuation and subtle sub-retinal pigment epithelium hyperreflective deposits (arrows).

FA will frequently show diffuse vascular leakage, late hyperfluorescence of sub-RPE lesions, punctate hyperfluorescent window defects and round, hypofluorescent lesions.

to the U.S. HIV epidemic.¹

Patients frequently present with symptoms of painless decreased visual acuity and floaters, or during a secondary evaluation after they've been diagnosed with PCNSL. While the anterior chamber typically shows nonspecific anterior uveitis with non-granulomatous keratic precipitates and variable levels of cell and flare, posterior segment findings include vitreous cells and sub-RPE infiltrates.

Without a history of PCNSL or the characteristic sub-RPE aggregates of lymphoma cells, the disease can be challenging to diagnose. It's frequently mistaken for a chronic, relapsing inflammatory disorder.

Multimodal imaging can be helpful in characterizing the disease. FA will frequently show diffuse vascular leakage, late hyperfluorescence of sub-RPE lesions, punctate hyperfluorescent window defects and round, hypofluorescent lesions.¹ FA in VRL only rarely shows petaloid leakage in the macula, a notable contrast to the cystoid changes that frequently occur in uveitis. The round, hypofluorescent spots surrounded by mottled hyperfluorescence can give the appearance described as a "leopard-spot" pattern.

OCT can show nodular deposits of accumulated lymphomatous cell depositions beneath the RPE, resulting in focal dome-shaped hyperreflective pigment epithelial elevations of medium intensity.² Fundus autofluorescence shows granular hyper- and hypoautofluorescence thought to be associated with active lymphoma.^{2,3}

Making the diagnosis

A high degree of suspicion is essential when signs suggestive of VRL present. Because of its similarity to other causes of posterior and intermediate uveitis, steroids are frequently prescribed initially. Because steroids are lymphocytic, signs and symptoms improve initially, but withdrawal of systemic steroids results in relapse of lymphocytic proliferation. To make a definitive diagnosis of VRL, intraocular biopsy with diagnostic vitrectomy confirms the presence of lymphoma.

Submitted specimens should include 1.5 to 2 mL of undiluted vitreous.⁴ If a subretinal aspirate or chorioretinal biopsy is collected, then the specimen should be promptly delivered to the laboratory for histological and cytopathological analysis. Cytokine analysis may also be ordered and classically shows elevated interleukin 10 (IL-10) levels or an increased IL-10 to IL-6 ratio in PVRL compared to patients with uveitis.⁵

Recent reports have described molecular genetic testing of aqueous and vitreous samples for the *MYD88 L265P* mutation in patients with suspected PVRL. *MYD88* is found in approximately 80 percent of PVRL, and with the use of droplet digital PCR, aqueous and vitreous testing for the mutation has a sensitivity of 67 and 75 percent, respectively, with essentially 100 percent specificity.^{6,7}

Treatments

Available treatments for VRL include

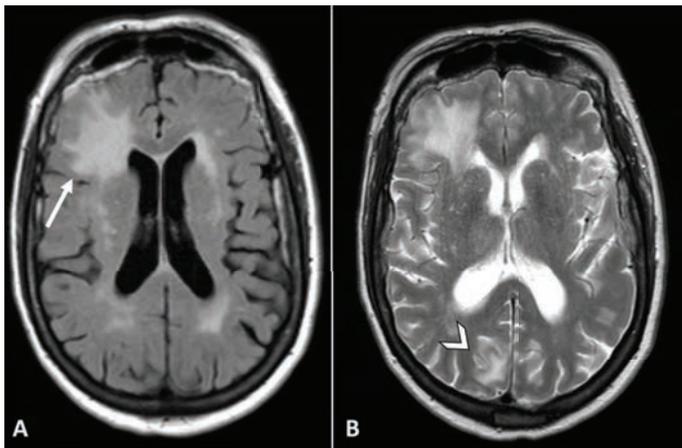


Figure 4. T1-weighted (A) and T2-weighted (B) MRI of the brain with and without contrast show a 1-x-1.7-cm right frontal (A, arrow) and 8-x-7-mm right occipital (B, arrowhead) cortical-based masses with extensive vasogenic edema consistent with central nervous system involvement of vitreoretinal lymphoma.

systemic chemotherapy, external beam radiotherapy (EBRT) and intravitreal chemotherapy. In cases of bilateral eye involvement or combined ocular and CNS disease, systemic chemotherapy is frequently undertaken in conjunction with a medical oncologist. The most common chemotherapies include high-dose intravenous methotrexate and cytarabine.¹

When the disease is restricted to the eye, local treatment, including EBRT or intravitreal chemotherapy, can be effective at inducing local remission and is similarly efficacious to systemic therapy in preventing recurrence.⁸ EBRT is highly effective, but its use must be weighed against the risk of local complications such as dry eye, cataract formation and radiation retinopathy.

Intravitreal injections of chemotherapy including methotrexate and melphalan have demonstrated local control of VRL over extended treatment protocols. Intravitreal rituximab has also been evaluated, but with higher relapse rates than other agents.⁹ All intravitreal injection-based protocols involve repetitive injections and the associated risk of ocular complications.

Bottom line

Primary vitreoretinal lymphoma is a rare and potentially fatal extranodal lymphoma that can present multiple diagnostic and therapeutic challenges. Due to its poten-

tial to involve the CNS and for delayed diagnosis due to non-specific findings, a high degree of suspicion must be maintained based on the clinical signs and patient demographics. Multimodal imaging can aid in the diagnosis of this challenging disease, but definitive diagnosis is made with intraocular biopsy. Treatment includes local and systemic therapies depending on the overall state of the disease, with VRL restricted to the eye frequently receiving injections of chemotherapy or EBRT. [®]

REFERENCES

1. Sagoo MS, Mehta H, Swamipillai AJ, et al. Primary intraocular lymphoma. *Surv Ophthalmol*. 2014;59:503-516.
2. Egawa M, Mitamura Y, Hayashi Y, Naito T. Spectral-domain optical coherence tomographic and fundus autofluorescence findings in eyes with primary intraocular lymphoma. *Clin Ophthalmol Auckl NZ*. 2014;8:335-341.
3. Casady M, Faia L, Nazemzadeh M, Nussenblatt R, Chan C-C, Sen HN. Fundus autofluorescence patterns in primary intraocular lymphoma. *Retina*. 2014;34:366-372.
4. Pulido JS, Johnston PB, Nowakowski GS, Castellino A, Raja H. The diagnosis and treatment of primary vitreoretinal lymphoma: A review. *Int J Retina Vitre*. 2018;4:18.
5. Pochat-Cotilloux C, Bienvenu J, Nguyen A-M, et al. Use of a threshold of interleukin-10 and il-10/il-6 ratio in ocular samples for the screening of vitreoretinal lymphoma. *Retina*. 2018;38:773-781.
6. Hiemcke-Jiwa LS, Ten Dam-van Loon NH, Leguit RJ, et al. Potential diagnosis of vitreoretinal lymphoma by detection of MYD88 mutation in aqueous humor with ultrasensitive droplet digital polymerase chain reaction. *JAMA Ophthalmol*. 2018;136:1098-1104.
7. Raja H, Salomão DR, Viswanatha DS, Pulido JS. Prevalence of MYD88 L265P mutation in histologically proven, diffuse large b-cell vitreoretinal lymphoma. *Retina*. 2016;36:624-628.
8. Grimm SA, Pulido JS, Jahnke K, et al. Primary intraocular lymphoma: An International Primary Central Nervous System Lymphoma Collaborative Group Report. *Ann Oncol Off J Eur Soc Med Oncol*. 2007;18:1851-1855.
9. Larkin KL, Saboo US, Comer GM, et al. Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. *Br J Ophthalmol*. 2014;98:99-103.

When the disease is restricted to the eye, local treatment, including external beam radiotherapy or intravitreal chemotherapy, can be effective at inducing local remission.

Avoid these pitfalls when ordering labs

More testing doesn't necessarily result in better patient care and can lead to unnecessary lab work.

By Brian K. Do, MD



Department Editor
Akshay S. Thomas,
MD, MS

Bios

Dr. Thomas is an associate in vitreoretinal surgery and uveitis at Tennessee Retina, with offices in central Tennessee and southern Kentucky.

Dr. Do specializes in surgical and medical diseases of the retina as well as in uveitis and ocular immunology. He is with the Retina Group of Washington and sees patients in Chevy Chase, Md., as well as in Fairfax and Tysons Corner, Va.

DISCLOSURE: Drs. Thomas and Do have no relevant financial relationships to disclose.

When it comes to appropriately diagnosing and managing complex ocular inflammatory disease, a healthy understanding of potential etiologies and how to formulate a differential diagnosis are of paramount importance. A focused workup removes hurdles on the way to disease treatment and, ultimately, quiescence.

I find too frequently that when evaluating patients with uveitis, physicians, both ophthalmologists and non-ophthalmologists alike, tend to order extraneous and unnecessary testing. Here, I'll explore a targeted approach to lab testing and review what tests should and shouldn't be ordered.

Three goals of lab testing

In my opinion, lab testing has three goals:

- Ensure we don't miss a systemic infection, and simultaneously "clear the way" for regional or systemic steroid therapy and potentially for steroid-sparing immunomodulatory treatment.
- Possibly lead to a new systemic diagnosis (related to or associated with the ocular disease), for which further workup and treatment may be necessary.
- Provide additional prognostic information on the disease process.

In discussing potential causes of ocular inflammatory disease, it's important to keep in mind that the goal of lab testing in patients with these conditions isn't intended so much to uncover a mystery diagnosis in an "ah-hah!" moment, but to guide therapy. We should resist the urge to test exhaustively until a test returns positive.

While some uveitis fits the diagnostic criteria for previously described entities or phenomena, many forms don't necessarily

look the way textbooks might lead you to believe. This doesn't mean, however, that the disease process won't respond equally well to pharmacotherapy.

Is there a 'standard' workup?

The short answer is no. The disease should be classified based on the clinical exam findings and a well-documented history; then decisions on testing can be made. For example, HLA-B27 testing is reasonable in the setting of acute anterior uveitis, especially if the patient tells you they have been experiencing lower back pain and stiffness. But, it would be less so in a patient who has an occlusive retinal vasculitis or otherwise undifferentiated panuveitis, scenarios in which HLA-B27 positivity wouldn't be expected. The workup should be tailored to the patient and their presentation.

The one condition for which testing is always reasonable, regardless of the type of inflammatory disease, is syphilis. This is the one easily curable cause of pretty much any form of uveitis, and a timely diagnosis can significantly reduce both ocular as well as systemic morbidities. Guidelines for syphilis testing include specific treponemal testing (i.e., fluorescent treponemal antibody absorption [FTA-Abs], *treponema pallidum* particle agglutination [TP-PA] assay, *T. pallidum* immunoglobulin G [IgG], various enzyme immunoassay tests, chemiluminescence immunoassays, immunoblots or rapid treponemal assays), as well as a standard nontreponemal test (i.e., rapid plasma regain [RPR], Venereal Disease Research Laboratory [VDRL]) with titers for monitoring treatment response.¹ In some cases of ocular syphilis, nontreponemal testing, such as RPR or VDRL may be negative in the presence of active disease.²

If you happen to live in an area where tuberculosis is endemic, specialized testing



Birdshot chorioretinopathy is a sign that the human leukocyte antigen test HLA-A29 is in order. Nearly every reported case of birdshot chorioretinopathy has occurred in HLA-A29-positive patients.

for TB may also be warranted. There is no perfect laboratory test, but interferon-gamma release assays such as QuantiFERON TB Gold (Quest Diagnostics) and the TB-spot test are reasonable options, the results of which previous bacilli Calmette-Guérin vaccination won't affect. A positive result may not indicate active TB uveitis (a positive assay and a simultaneous and unrelated immune-mediated process is more likely), but it can be helpful, especially before initiating systemic immunosuppressive agents such as adalimumab (Humira, AbbVie) or infliximab (Remicade, Janssen).

Human leukocyte antigen typing

There's little reason not to order HLA-B27 testing in patients with anterior uveitis, especially in those with an alternating, acute disease pattern. It is well accepted that 7 to 8 percent of the general population (without disease) will demon-

strate HLA-B27 positivity, so you need to consider the possibility of anterior uveitis and an unrelated positive HLA-B27 allele as well.

The only other human leukocyte antigen test that has any clinical value is HLA-A29 in the setting of birdshot chorioretinopathy (*Figure*) or an inflammatory/infiltrative chorioidopathy with a similar phenotype. Nearly every reported case of birdshot chorioretinopathy has occurred in HLA-A29-positive patients. Some uveitis specialists don't believe that seronegative (HLA-A29-negative) birdshot chorioretinopathy exists. A positive test in an individual with bilateral, yellow-orange ovoid chori-

dal spots essentially confirms the diagnosis, whereas a negative test may lead one to consider other diagnoses, such as lymphoma and sarcoidosis, both of which can closely mimic birdshot.

Tests to Omit

This list includes:

- *Angiotensin-converting enzyme, lysozyme and gallium scan.* One of my mentors frequently reminded us as trainees that the positive predictive value of any one of these examinations in diagnosing sarcoidosis is 20 to 25 percent. A quick review of the pulmonary literature confirms this.³ At best with a positive test, one is likely to incorrectly diagnose sarcoidosis three out of four times. A chest X-ray or CT-scan is more likely to demonstrate hilar adenopathy in the setting of true sarcoidosis. Which of these should be ordered first is somewhat controversial; the decision is

There's no standard work-up for uveitis. The disease should be classified based on the clinical exam findings and a well-documented history; then decisions on testing can be made.

ultimately up to the patient and the practitioner ordering the test.

- **Serologic testing for Herpesviridae and Toxoplasma.** The results of these tests (immunoglobulin M or IgG for HSV 1 and 2, VZV, CMV, *Toxoplasma gondii*) are helpful only when negative. The rates of seropositivity in the general population are too high to help with diagnosis of anterior and posterior uveitis and panuveitis in which the clinician suspects an infectious etiology. My feeling is that acquiring ocular fluid and PCR analysis is absolutely necessary to rule out or confirm any one of these organisms as the causative agent in ocular inflammatory disease. I typically prefer an aqueous paracentesis (when anterior chamber inflammation is present), but obtaining a specimen via the pars plana may be indicated when pursuing surgery.

- **Antinuclear antibody (ANA).** Clinical scenarios exist in which undiagnosed lupus should be explored as a potential underlying diagnosis: scleritis; ulcerative keratitis; occlusive retinal vasculitis; and inflammatory choroiditis. An ANA, especially in children with anterior uveitis and juvenile idiopathic arthritis, can provide valuable prognostic information. However, in adults, seropositivity can reach as high as 15 percent, and while a positive test may be suggestive of lupus, other clinical findings are necessary to make a diagnosis.

- **Rheumatoid factor, antineutrophil cytoplasmic antibody (ANCA).** I would include this only in cases of scleritis, ulcerative keratitis or retinal vasculitis. Rheumatoid arthritis is not typically associated with uveitis as is the case for ANCA-associated vasculitides.

Get it right the first time

It's difficult to articulate a good reason for not testing after the first episode. The ability to identify an underlying condition with potential systemic morbidity is always

It's difficult to articulate a good reason for not testing after the first episode. The ability to identify an underlying condition with potential systemic morbidity is always of value.

Do's and don'ts for ordering lab tests to work up uveitis

Do's

- Syphilis testing
- TB testing (granulomatous disease; individuals from endemic regions; prior to TNF-alpha inhibition)
- Chest X-ray / chest CT (especially in granulomatous disease)
- HLA-B27 (in anterior uveitis)
- HLA-A29 (in appropriate cases of posterior uveitis)

Don'ts

- Angiotensin converting enzyme (ACE) / lysozyme / Gallium scan
- Antinuclear antibody (ANA, except in pediatric anterior uveitis, scleritis, PUK, retinal vasculitis)
- Rheumatoid factor (RF) / anti-cyclic citrullinated peptide (CCP) / antineutrophil cytoplasmic antibody (ANCA, except in scleritis, PUK, retinal vasculitis)
- Erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP, unless significant suspicion for giant cell arteritis)
- Other human leukocyte antigen testing

of value. Theoretically, it's better to know early on about these types of scenarios than to allow an infectious or systemic process to declare itself over time.

Being able to provide prognostic information about associated systemic morbidity and likelihood of recurrence alone is reason enough to warrant checking for HLA-B27 positivity in these patients. The SENTINEL study has shown that if a patient is HLA-B27 positive and experiences sudden-onset anterior uveitis, the likelihood of having or developing spondyloarthritis is 90 percent.⁴ Those of us who have seen patients with severe spondyloarthritis in the setting of HLA-B27-associated recurrent acute anterior uveitis, I'm sure, would love to turn back the clock and implement treatment with disease-modi-

THE RIGHT ROUTE CAN MAKE ALL THE DIFFERENCE



Access retinal disease directly through the suprachoroidal space.

The suprachoroidal space provides a novel approach to drug delivery, offering new opportunities to access diseased tissue in the back of the eye.¹

▶ See the potential at SuprachoroidalSpace.com

Reference: 1. Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. *Adv Drug Deliv Rev.* 2018;126:58-66.

MMM-0038 02/19

© 2019 Clearside Biomedical, Inc.

ying agents to prevent these types of problems from occurring in the first place.

Every episode of uveitis should be seen as an opportunity to recognize and diagnose associated conditions, but it's equally important to acknowledge that this may not take place in many cases.

Why we should order testing

Many physicians question who should order the testing for the uveitis workup; if it should be the primary care physician or rheumatologist. When we don't order our own testing, patients frequently end up undergoing analyses that likely have no impact on or relevance to their disease.

Many non-ophthalmologists (and some ophthalmologists) have difficulty formulating a reasonable differential diagnosis when it comes to ocular inflammatory disease. There seems to be a tendency to over-order testing but to neglect some of the infectious testing that could help inform treatment.

I frequently see patients that have previously been seen by physicians both within and outside of my practice, and that have been subsequently referred to a rheumatologist for a "uveitis workup." It seems a bit unfair and unreasonable for us to expect that a practitioner with little understanding of these disease processes and how to interpret our exam findings should be able to perform focused, appropriate testing without proper guidance.

When in doubt, a quick e-mail or phone call to an accessible uveitis specialist can provide some valuable insight, especially if the individual initiating the workup is not uveitis fellowship-trained and/or uncomfortable making these types of decisions.

Cost-benefit analysis of testing

Several years ago, a study of diagnostic testing practices amongst members of the Executive Committee of the American Uveitis Society (AUS) was conducted. Be-

cause there are no guidelines for testing, the results showed a great deal of variation in how testing is performed in a number of different clinical scenarios.⁵

In calculating the associated costs, the study found that, not surprisingly, radiologic and ophthalmic imaging (not discussed in depth here) are among the most expensive tests ordered, comprising more than half of the testing costs when facility and professional fees are taken into account. A brain MRI, which can be invaluable in ruling out concomitant central nervous system disease in cases of intraocular lymphoma or demyelinating disease in individuals with intermediate uveitis, can cost thousands of dollars. On the other hand, serologic testing, like that for syphilis and QuantiFERON assays, cost around \$100 or less. Therefore, we should seriously consider the clinical utility of testing, especially that of radiologic imaging, before sending an order.

Bottom line

It's important in these situations to think to oneself, "How will these results change the management of this individual's disease?" More testing simply does not result in better patient care and, in my opinion, often leads to unnecessary additional testing and misuse of resources. 

REFERENCES

1. Syphilis pocket guide for providers. Document CS275410-A. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; Atlanta, GA. Available at: <https://www.cdc.gov/std/syphilis/Syphilis-Pocket-Guide-FINAL-508.pdf>
2. Tamesis SS, Foster CS. Ocular Syphilis. *Ophthalmology*. 1990;97:1281-1287.
3. Ungrasert P, Carmona EM, Crowson CE, Matteson EL. Diagnostic utility of angiotensin-converting enzyme in sarcoidosis: A population-based study. *Lung*. 2016;194:91-95.
4. Juanola X, Loza Santamarie E, Cordero-Coma M. SENTINEL Working Group. Description and prevalence of spondyloarthritis in a large cohort of patients with anterior uveitis: The SENTINEL Interdisciplinary Collaborative Project. *Ophthalmology*. 2016;123:1632-1636.
5. Lee CS, Randhawa S, Lee AY, Lam DL, Van Gelder RN. Patterns of laboratory testing utilization among uveitis specialists. *Am J Ophthalmol*. 2016;170:161-167.

A brain MRI can cost thousands of dollars. On the other hand, serologic testing, like that for syphilis and QuantiFERON assays, can cost around \$100 or less.

Pearls for RD repair after ruptured globe

Ten tips to help in the preparation and execution of these often complicated cases.

Retinal detachments occur in about one out of every four eyes with a ruptured globe, typically days to weeks after the initial injury. They are often associated with vitreous hemorrhage, as well as choroidal hemorrhage or detachment, which can make surgical planning and the surgery itself more complicated.

Here we offer 10 suggestions we've found useful in the management of these complex patients.

1. Do a careful preoperative exam. Anticipate potential difficulties (e.g., limited anterior view secondary to corneal sutures, site of rupture where you might normally place your infusion) and plan appropriately.

Ultrasonography the day or morning before surgery can be helpful to assess the presence of choroidal detachments and to evaluate the location of the retinal detachment, which may change from the time of diagnosis to surgery. Recognize that there may be incarcerated retina within a posteriorly ruptured site. Read the operative report from the initial surgery.

2. Start by thoughtfully placing your infusion. If you have no view of the posterior pole, place an anterior infusion, either with an anterior chamber maintainer or a small-gauge microcannula placed at the limbus.

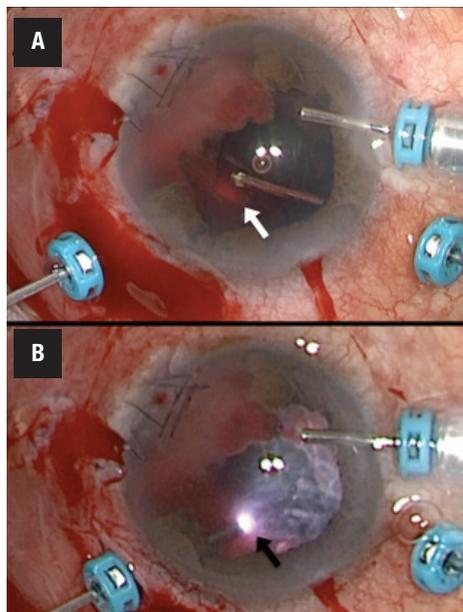
3. Work from front to back. Begin by clearing your view anteriorly by whatever means necessary—scrape the cornea, wash out the anterior chamber, remove the traumatic cataract.

View the Video



Drs. Kaden and Modi demonstrate some of their 10 tips for surgery to repair retinal detachments after a ruptured globe injury.

http://bit.ly/VideoPearl_013



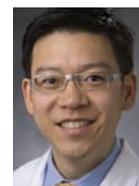
With a 4-mm microcannula placed in the suprachoroidal space (A), a glowing red reflex (white arrow) is visible when the light pipe is placed into the cannula, but no instrument is visible. Use caution in these situations; have a low threshold for removing and replacing the cannula. After a longer, 6-mm cannula is inserted, both the cannula and light pipe (B, black arrow) are visible in the vitreous cavity.

4. When you have a view of the vitreous cavity, make your posterior sclerotomies. Be careful; shallow choroidal detachments or suprachoroidal hemorrhage, often accompanied by vitreous hemorrhage that obscures the view, puts an eye at risk for inadvertent placement of a cannula in the suprachoroidal space, especially into a soft eye.

It may be helpful to replace a standard 4-mm cannula with a longer 6-mm cannula, available in some systems. Be vigilant to avoid trimming what may be retina or choroid masquerading as vitreous overlying the cannula.

(Continued on page 27)

By Talia R. Kaden, MD, and Yasha S. Modi, MD



Department Editor
Paul Hahn, MD, PhD

Bios

Dr. Hahn is a partner at NJ Retina in Teaneck, N.J. Dr. Kaden is an assistant professor at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Garden City, N.Y. She is based out of Manhattan Eye, Ear and Throat Hospital, New York.

Dr. Modi is an assistant professor in the department of ophthalmology at New York University and is the director of uveitis and tele-retina there.

DISCLOSURES: Dr. Hahn is a consultant to Alcon. Dr. Modi is on the advisory boards of Alimera, Allergan, Genentech and Novartis. Dr. Kaden has no disclosures

Focus on Surgery

Peripheral vitrectomy without an assistant

A device that combines a light pipe and a scleral depressor can enhance viewing with or without a digital microscope.



Bozho Todorich,
MD, PhD

Bozho Todorich, MD, PhD

Take-home points

- » Endoillumination with chandelier systems are adequate for many cases, but the illumination of the retina can be uneven and static, and carries risk of iatrogenic lens injury and can add significant cost per case.
- » Scleral transillumination with digital microscope platforms is safe and effective, but these platforms are not yet widely adopted.
- » A low-cost illuminated scleral depressor allows the surgeon to depress and transilluminate the eyewall for unassisted peripheral vitrectomy with a digital or traditional operating microscope.
- » Intravitreal Triescence can enhance visibility of the vitreous when using scleral depression-transillumination.

Over the past four decades we've witnessed unprecedented advances and innovation in vitreoretinal surgery.¹ Current vitrectomy platforms have automated most parts of vitrectomy surgery, such that surgeons nowadays can perform steps such as fluid-air exchange, viscous fluid injection of silicone oil and laser retinopexy independently, efficiently and unassisted, with controls for all of these steps being at our fingertips (and toe tips).^{1,2}

Yet, when it comes to peripheral vitrectomy, particularly vitreous base shaving, many surgeons still rely on skilled assis-

tants to provide scleral indentation the same way we did when pars plana vitrectomy first started more than 40 years ago.

Here, I describe a technique that uses a scleral depressor-transilluminator to provide excellent visualization of the peripheral retina for unassisted peripheral vitrectomy.

In some settings, retina surgeons are surrounded by bright and eager assistants, surgical retina fellows and ophthalmology residents who can provide scleral depression, particularly in cases where good vitreous base shaving is desired, such as when performing a repair of a rhegmatogenous retinal detachment.

For many of us in private practice, where trainee surgeons aren't readily available, the options include training scrub technicians to perform scleral depression or using an endoilluminating chandelier system. But while both of these approaches can be effective, each has its unique challenges and drawbacks.

Bio

Dr. Todorich practices with Pennsylvania Retina Specialists PC in Camp Hill.

DISCLOSURES: Dr. Todorich disclosed financial relationships with Vortex Surgical, Genentech, Allergan and Regeneron Pharmaceuticals.

View the Video



Dr. Todorich demonstrates his technique for performing illuminated scleral depression without an assistant during peripheral vitrectomy. Available at: http://bit.ly/RetSpecMag_09201901

[RetSpecMag_09201901](http://bit.ly/RetSpecMag_09201901)

Limits of endoillumination

A number of commercially available chandelier systems are compatible across vitrectomy platforms.³⁻⁵ While endoillumination with these devices can be adequate in many cases,⁶ the illumination of the retina is far from uniform. With the chandelier, parts of the peripheral retina are well-illuminated while other parts remain in the dark, and peripheral vitrectomy with less-than-ideal illumination of the retina increases the risk of iatrogenic breaks.

In addition, glare can hamper vitrectomy within a few clock hours of the chandelier device. Chandelier depression in a phakic eye raises the risk of lens touch and iatrogenic cataract, which, although rare, would be a very unwelcome complication.

Lastly, the price of a chandelier system is not insignificant, particularly for surgeons operating at increasingly cost-conscious ambulatory surgical centers. Our surgical technicians can learn to perform scleral depression for vitrectomy that rivals that of ophthalmology residents and beginning retina fellows. Yet, most community hospitals and ASCs don't have dedicated surgical eye teams, thus making access to trained assistants inconsistent at best.

It's not uncommon for community retina surgeons to walk into the operating room and find that the assigned assistant for the day is a surgical tech with minimal or no ophthalmology and retina experience. Attempting to perform depressed vitrectomy with an inexperienced assistant in that setting is unsafe and ill-advised.

All these issues have created the need for a technique and device that would transfer the depressor for vitreous base shaving from the hands of an unskilled assistant to the hands of the surgeon. As such, this would not only enhance the surgeon's satisfaction and independence, but also improve patient safety.

Scleral transillumination

Scleral transillumination is not a novel technique. It has been and continues to be

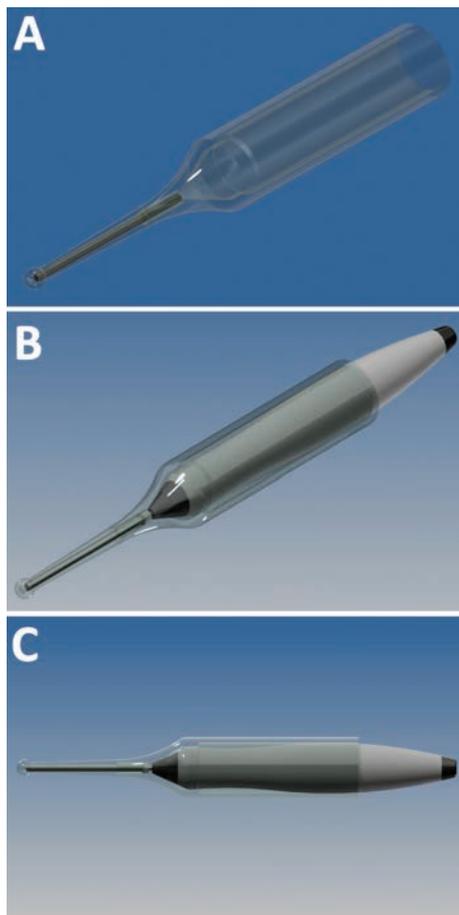


Figure 1. The light pipe is inserted into the back end of the scleral depressor (A) and glides into position (B) where the tip of the light ends up at the inside of the distal depressor tip (C) once it's fully seated.

used in ocular oncology for localization of intraocular tumors and optimization of radioactive plaque placement. Yet, its use in intraocular surgery hasn't gained traction.

We recently published a small pilot study evaluating the technique of using endoillumination light pipe in a scleral depressor-transilluminator in conjunction with Alcon's NGenuity 3D system.⁷ We found that scleral depression-transillumination with the light pipe was safe and effective for performing peripheral vitrectomy in a majority of the patients with common vitreoretinal surgical indications (*Video*). Caucasian myopic eyes with thinner sclera

Scleral transillumination highlights the anatomy of the eye wall very well. It has been used extensively in ocular oncology for tumor localization and optimization of radioactive plaque placement.

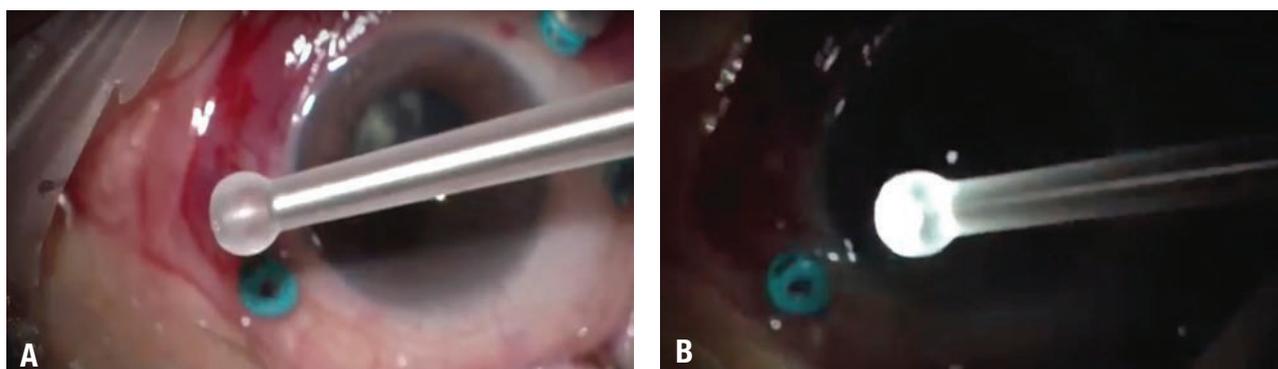


Figure 2. The scleral depressor tip with the light pipe inserted (A) and illuminated (B).

and lightly pigmented fundi appeared to be the best candidates.

The advantage of using this technique with a digital microscope is the ability to enhance endogenous luminance, extend the depth of field and allow for manipulation of the color channels to potentially enhance the Tyndall effect and visualization of the peripheral vitreous gel.⁸

The adapter allows conversion of any gauge light pipe into a scleral depressor-transilluminator, allowing surgeons to perform unassisted peripheral vitreous base shaving.

Alternative to digital microscope

Considering that digital microscope platforms like NGenuity are still not widely available, particularly at community-based retina practices, we designed a device adapter for endoillumination light pipe that would allow conversion of any gauge light pipe into a scleral depressor-transilluminator and allow it to be used with any analogue operating microscope (Figure 1, page 21).

The device is made of inert polycarbonate molded into the shape of a traditional ball-point depressor. Its stiffness and feel approach that of a regular scleral depressor. To further enhance its stiffness and reduce light backscatter and glare, the shaft of the depressor is fortified with a 19-ga. hypodermic needle.

The light pipe is inserted into the back end and glides into position where the tip of the light ends up at the inside of the distal depressor tip once it's fully seated (Figures 1 and 2). For optimal viewing, the illumination on the vitrectomy machine is adjusted to the maximum setting. The

depressor tip is machined to achieve maximum optical clarity while its polished ball tip glides seamlessly along the scleral surface, even for patients with tighter orbits. The surgeon performs unassisted vitrectomy with one hand while depressing and transilluminating simultaneously with the other (Video). The device I use is produced and marketed by Vortex Surgical. While the Vortex surgical device is designed to be used with the Alcon system, similar devices are available for other platforms, such as the DORC Eva system.

The chief advantage of this technique is that it gives the retina surgeon absolute control of the eye during peripheral vitrectomy, a surgical step that had traditionally required trained assistants. Use of the adapter device allows conversion of any gauge light pipe into a scleral depressor-transilluminator, providing the required stiffness and glare reduction, and eliminating the chance of scleral wall perforation—a risk if the light pipe alone were to be used. It achieves this at a fraction of the cost of a traditional chandelier.

Navigate the learning curve

With this technique, the anatomy of the retina, retinal pigment epithelium and choroid is well-visualized, allowing for detection of even small retinal breaks. Like any new technique, there's a learning curve of approximately five to 10 cases to get the "feel" for it and gain comfort with a view that's different from traditional endoillu-

mination. The view is best in thin-walled, blonde, myopic Caucasian eyes, but can be challenging in highly pigmented fundi.

Although the vitreous itself may be challenging to visualize directly, as with traditional endoilluminated depressed vitrectomy, adjuvants such as intravitreal Triescence can enhance visibility.

Methodical removal

You must be methodical when removing the vitreous, doing it one clock hour at a time, starting at the posterior edge of the vitreous base and moving anteriorly, ensuring complete vitreous removal before moving to the adjacent clock hour. This will ensure complete peripheral vitrectomy without skipping any areas, particularly in cases such as retinal detachment repair.

Bottom line

Using a light pipe in conjunction with the illuminated scleral depressor allows for visualization of the peripheral retina with depression during vitrectomy without relying on an assistant. It allows unassisted vitrectomy with both digital and traditional microscopes. Cheaper than a chandelier system, the illuminated depressor promotes patient safety and the surgeon's independence while also helping to reduce the cost of each case. 

REFERENCES

1. Fujii GY, De Juan E Jr, Humayun MS. A new 25-gauge instrument system for transconjunctival sutureless vitrectomy surgery. *Ophthalmology*. 2002;109:1807-1812.
2. Oshima Y. Choices of wide-angle viewing systems for modern vitreoretinal surgery: A semi-quantitative evaluation of the visual angle field and imaging contrast. *Retina Today*. 2012;5:37-42.
3. Eckardt C, Eckardt T, Eckardt U. 27-gauge Twilight chandelier illumination system for bimanual transconjunctival vitrectomy. *Retina*. 2008;28:518-519.
4. Sakaguchi H, Oshima Y, Nishida K, Awh CC. A 29/30-gauge dual-

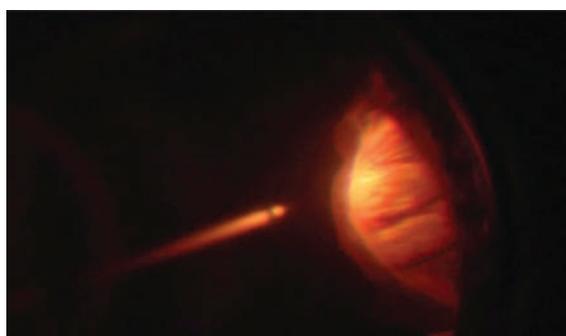
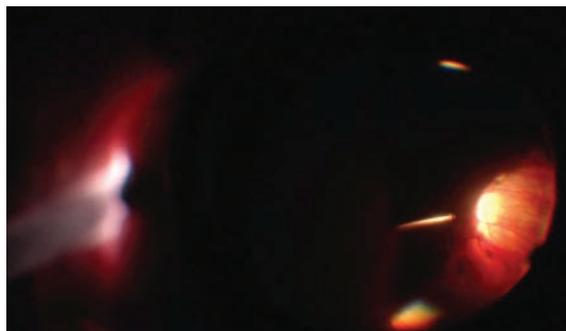


Figure 3. Three different views of the peripheral retina. Illumination on the vitrectomy machine on the maximum setting gives optimal viewing with transillumination, with one hand holding the scleral depressor and the other the vitrector probe.

chandelier illumination system for panoramic viewing during microincision vitrectomy surgery. *Retina*. 2011;31:231-233.

5. Oshima Y, Awh CC, Tano Y. Self-retaining 27-gauge transconjunctival chandelier endoillumination for panoramic viewing during vitreous surgery. *Am J Ophthalmol*. 2007;143:166-167.

6. Leiderman YI. Endoillumination without an assistant: A technique to perform peripheral vitreoretinal surgery with chandelier endoillumination independently. *Retina Specialist*. 2018;1:34-35.

7. Todorich B, Stem MS, Hassan TS, Williams GA, Faia LJ. Scerla transillumination with digital heads up display: A novel technique for visualization during vitrectomy surgery. *Oph Surg Lasers Imag Retina*. 2018;49:436-439.

8. Veckeneer M, Wong D. Visualising vitreous through modified trans-scleral illumination by maximising the Tyndall effect. *Br J Ophthalmol*. 2009;93:268-270.

9. Peyman GA, Canakis C, Livir-Rallatos C, Easley J. A new wide-angle endoillumination probe for use during vitrectomy. *Retina*. 2002;22:242.

You must be methodical when removing the vitreous, proceeding one clock hour at a time, starting at the posterior edge of the vitreous base and moving anteriorly.

Focus on Surgery

Rethinking routine use of steroid drops after surgery

*Why do we use postop drops the way we do?
The case for subconjunctival triamcinolone.*

Elizabeth Atchison, MD, and John Pollack, MD



Elizabeth Atchison, MD



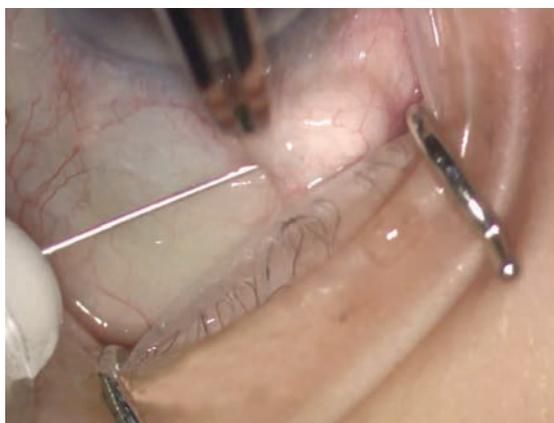
John Pollack, MD

Take-home points

- » Patients don't like eyedrops and have difficulty using them after ocular surgery.
- » Retina surgeons agree that steroids after surgery are necessary to reduce inflammatory complications.
- » Data suggest that a single 4-mg dose of subconjunctival triamcinolone acetate is a reasonable alternative to a traditional steroid drop taper plus a subconjunctival injection of 1-mg dexamethasone at the end of a case.

While there is no established standard of care for postoperative drops, a common regimen is an antibiotic drop four times a day for a week, a cycloplegic drop twice a day for a week and a steroid drop starting four times a day and tapering off over a period of four to six weeks. The rationale is that antibiotics lower the risk of infection, cycloplegics lower the risk of posterior synechiae and pain, and steroids reduce the risk of inflammatory sequelae such as pain, photophobia, fibrin and synechiae.

However, the literature lacks support for the clinical efficacy of this approach, and some cataract surgeons have started moving away from routine use of postoperative drops with good results. A similar approach may succeed in vitreoretinal surgery. Here, we discuss our own work that has shown the potential benefits of a subconjunctival triamcinolone injection after vitreoretinal surgery.



Subconjunctival triamcinolone injection is convenient and doesn't induce postoperative floaters. (Courtesy Neal H. Shorstein, MD)

The burden of postoperative drops

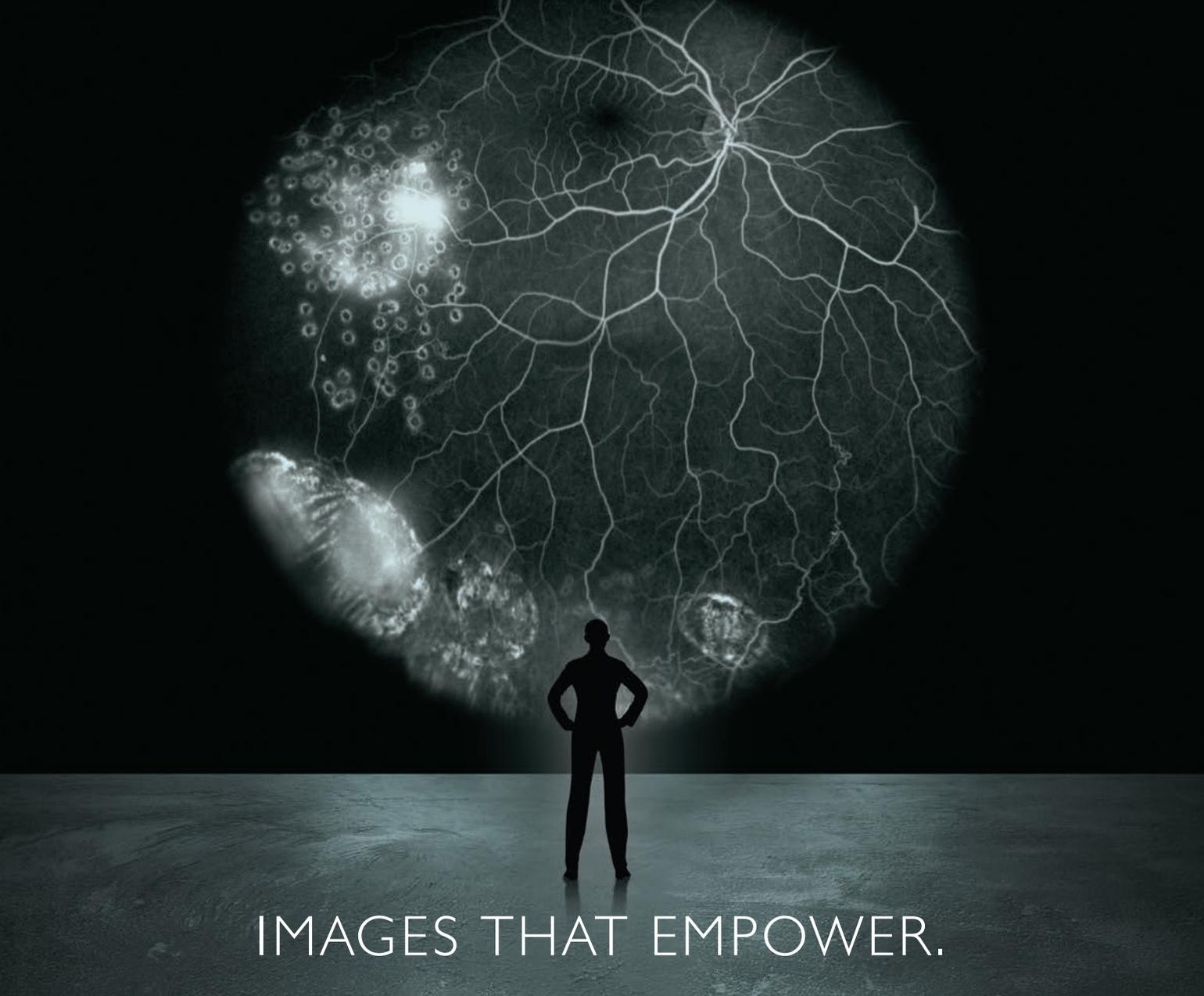
An informal survey of 41 U.S. retinal specialists queried on their routine peri- and postoperative use of ocular steroids found that all respondents (41 of 41) prophylactically treat postoperative inflammation with some form of steroid after surgery (J. Pollack, personal communication June 2018). Ninety-eight percent (40 of 41) reported using postoperative

Bio

Dr. Atchison practices at Ophthalmology Ltd. in Sioux Falls, S.D.

Dr. Pollack practices at Illinois Retina Associates in Joliet and Hinsdale.

DISCLOSURE: Drs. Atchison and Pollack have no relevant financial relationships to disclose.



IMAGES THAT EMPOWER.



Welcome to a platform where every image is remarkably accurate. Reliably repeatable. Proven to enable confident clinical decision-making. And ready for the advanced image analytics necessary for success in a changing healthcare environment. It's a platform like none other. And now, one that's accessible for any practice.

Experience powerful images that empower you to do more for your patients and your practice. Experience Heidelberg Image Quality™.

To learn more, please call 800-931-2230 or visit [HeidelbergEngineering.com](https://www.HeidelbergEngineering.com)

This study suggests that a single subconjunctival injection of 4-mg triamcinolone acetonide at the end of retina surgery cases may be equal to 1 mg subconjunctival dexamethasone plus a topical steroid taper.

steroid drops, with 68 percent (28 of 41) supplementing steroid drops with a subconjunctival steroid injection at the end of surgery.

Most (83 percent, 33 of 40) stated that they place patients on a prolonged steroid taper starting at four times a day and tapering over a four to six weeks. The single surgeon who didn't use drops was using a single subconjunctival injection of 4 mg triamcinolone acetonide at the end of each case, regardless of case complexity, without subsequent steroid drops.

Postoperative drops are a known burden for patients. In addition to their expense, many patients lack the visual acuity and/or dexterity to reliably get drops in their eye, requiring another person to help them. Studies in the cataract literature have found a compliance rate lower than 10 percent for those having surgery for the first time, with the most common errors being missing the eye, contamination of the bottle tip and using an incorrect number of drops.¹

Design of our study

Recently, some cataract surgeons have started seeking an alternative to the routine use of postoperative drops, with good clinical outcomes and excellent patient acceptance.² In our retrospective case review study, we examined whether vitreoretinal surgeons may also be able to lessen the postoperative eye drop burden by eliminating the traditional postoperative steroid drop taper. This would decrease the time patients are on drops by 75 to 83 percent, and decrease the total number of drops after surgery by over 60 percent compared with the traditional drop regimen.³

In this study, we compared all patients of two surgeons undergoing vitreoretinal surgery during the study period. One surgeon routinely used a single subconjunctival injection of 4-mg triamcinolone acetonide at the end of the case (intervention group), while the other used 1 mg subconjunctival injection of dexameth-



Little evidence supports the efficacy of drops after ocular surgery, and some cataract surgeons are moving away from their routine use.

asone at the end of the case plus a traditional one-month topical steroid drop taper (control group). Patients who were on steroids within a week before surgery or who lacked at least 90 days of follow-up were excluded. Patients in both groups were also prescribed 1% atropine eye-drops b.i.d. and antibiotic drops (moxifloxacin unless contraindicated by allergy) q.i.d. Other eye drops were prescribed if indicated by individual patient course at the surgeon's discretion.

The control group consisted of 163 surgeries in 146 patients, the intervention group 161 surgeries in 135 patients. Demographics between the two groups were similar in terms of gender, age, or preoperative diagnosis of glaucoma or steroid responsive ocular hypertension.

The most common types of retinal surgery were vitrectomy (37 percent of controls and 29 percent of intervention group cases) and vitrectomy plus C3F8 gas (23 percent and 30 percent, respectively). Scleral buckles, vitrectomy/buckles and vitrectomy with oil comprised 12 and 15 percent of the respective totals. There were no statistically significant differences in the types of surgery between the control and intervention groups (*p*-values between 0.1 and 0.84).



No difference in IOP

There was also no statistically significant difference in intraocular pressure-related outcomes between the intervention and control groups, with 12 and 16 percent in the respective groups requiring additional IOP-lowering drops postoperatively ($p=0.08$). Twelve percent of controls and 16 percent in the intervention group developed IOP >29 mmHg during the postoperative period ($p=0.31$), and 14 and 20 percent, respectively, had an IOP increase ≥ 10 mmHg postoperatively ($p=0.12$).

New posterior synechiae and anterior chamber cell at one week were rare in both groups at less than 1 percent. Five percent of patients in the intervention group received supplemental postoperative steroid drops due to anterior chamber cell.

In both groups, IOP-related complications were more common in those with a history of glaucoma or steroid response before surgery, with 21 percent of the former and 44 percent of steroid responders developing IOP > 29 mmHg postoperatively vs. 12 percent without such a history. Similarly, 42 percent of those with a history of glaucoma and 44 percent with a history of steroid response had an IOP increase of ≥ 10 mmHg during the postoperative period compared with 12 percent without such a history.

What this study adds to our knowledge

The results of this study suggest that a single subconjunctival injection of 4 mg triamcinolone acetonide at the end of retina surgery cases may be equal in effectiveness and safety to 1 mg subconjunctival dexamethasone plus a one-month topical steroid taper. There was no evidence of increased risks of IOP-related

complications or inflammatory complications associated with the single injection. Regardless of the type of steroid used, patients with a history of glaucoma or IOP response were at higher risk of elevated IOP after vitreoretinal surgery.

Limitations

Because this was a case-review study, systemic differences in the patient populations may exist between the two surgeons, despite them operating out of the same offices. There was no protocol for when IOP drops were added after surgery and the surgeons may have differed in their thresholds for starting such drops. Similarly, there was no criteria for which patients received supplemental steroid drops after surgery in the intervention group.

Other surgeons may have higher or lower rates of supplemental drop use depending on their individual threshold. Both surgeons operated in sites that routinely added 10 mg of dexamethasone to the vitrectomy infusion solution, which may alter the rates of inflammatory complications compared to surgeons who do not routinely add steroid to the infusion.

Bottom line

A single subconjunctival of 4 mg triamcinolone acetonide at the end of retina surgery cases is a reasonable alternative to subconjunctival injection of 1 mg dexamethasone at the end of the case plus a traditional steroid drop taper. 

REFERENCES

1. An JA, Kasner O, Samek DA, Levesque V. Evaluation of eyedrop administration by inexperienced patients after cataract surgery. *J Cataract Refract Surg*. 2014;40:1857-1861.
2. Lindstrom RL, Galloway MS, Grzybowski A, Liegner JT. Dropless cataract surgery: An overview. *Curr Pharm Des*. 2017;23: 558-564.
3. Atchison EA, Gilca M, Civantos JM, Pollack JS. Elimination of steroid drops after vitreoretinal surgery. *Journal of vitreoretinal diseases*. In press 2019.

RD repair for ruptured globe

(Continued from page 19)

5. Once both instruments are safely in the vitreous cavity, slowly clear dense hemorrhage, cautiously proceeding anterior to posterior until the retina is visualized. At this point a posterior infusion may be placed. Apply similar caution to directly visualize the infusion line and avoid placement in the suprachoroidal space. As noted above, a longer 6-mm cannula can be helpful in this situation.

6. If the retina is incarcerated or extensive proliferative vitreoretinopathy membranes are present, a posterior retinectomy is often needed. Peel all membranes from posterior to anterior prior to performing a generous relaxing retinectomy. Remember that in these eyes, the PVR may be both preretinal and subretinal.

7. Perfluorocarbon liquids can be helpful. PFCLs can be used both for stabilizing the posterior retina and for displacing subretinal blood.

8. Once a relaxing retinectomy has been performed, these cases can be approached like a giant retinal tear. Bring the PFCL up past the retinectomy edge to allow for placement of a laser barricade and an air-fluid exchange.

9. Silicone oil is often the tamponade of choice given its stability and duration.

10. Follow the patients closely for the development of PVR reattachment.

Good luck! 

REFERENCES

1. Strykowski TP, Andreoli CM, Elliott D. Retinal detachment after open globe injury. *Ophthalmology*. 2014;121:327-333.
2. Nowomiejska K, Chorągiewicz T, Borowicz D, et al. Surgical management of traumatic retinal detachment with primary vitrectomy in adult patients. *J Ophthalmol*. 2017;2017:5084319.
3. Orban M, Islam YFK, Haddock LJ. Timing and outcomes of vitreoretinal surgery after traumatic retinal detachment. *J Ophthalmol*. 2016;2016:4978973.

Strategies to **reduce errors** in office procedures

A review of patient safety challenges in the retina practice and steps to eliminate procedure errors.



Kevin
Broderick, MD



Joshua D.
Levinson, MD



Daniel M
Berinstein, MD

Kevin Broderick, MD, Joshua D. Levinson, MD, and Daniel M. Berinstein, MD

Take-home points

- » Prevention of clinic-based “never events” should be a high priority for retina specialists, with every effort made to implement standards and processes to prevent such errors.
- » The retina specialist must manage a multitude of distractions in a setting almost predisposed to errors.
- » Electronic health records may be a source of “upstream” errors and carry-forward information must be up to date and accurate.
- » Standardized safety protocols for procedures should be modified and implemented within office-based settings.

Wrong-site, wrong-procedure, wrong-patient errors—also known as WSPEs—are “never events.” These errors can be devastating to patients and suggest fundamental flaws in safety procedures.¹

The incidence of wrong-site surgery in the operating room across all surgical specialties is estimated to be one event per 100,000 to 112,994 procedures, but is likely higher due to underreporting.^{2,3} This doesn’t include procedures performed in other settings, such as ambulatory surgery centers or interventional radiology services.⁴ In fact, a retrospective review of all surgical events over three years in the Veterans Health Administration system found that up to half of procedure-related adverse events occur in settings outside the OR.⁵ In that study, ophthalmology had the second highest rate of adverse events.

Given the high volume and frequency of procedures performed outside the OR in office-based retina practices, the prevention of clinic-based WSPEs should be

a high-priority focus in the specialty, with every effort made to implement standards and processes to prevent such errors. Here, we review patient safety challenges in office settings and describe steps for reducing and eliminating WSPEs.

Challenges in the clinic

Estimates of WSPEs in clinic-based settings aren’t readily available. Certain key differences between the OR and clinic setting may make the clinic an even higher risk environment for procedural errors. Most ORs have strict, established guidelines and protocols with institutional and, often, national oversight.

Subsequent checks and verifications help minimize the incidence of adverse events. For instance, nurses preoperatively typically verify the patient’s information, type of surgery and laterality with the patient, and corroborate this information with the consent form. The surgeon typically marks the surgical site, while simultaneously verbally confirming with the

Bio

Drs. Broderick, Levinson and Berinstein are with the Retina Group of Washington in Chevy Chase, Md.

DISCLOSURES: Drs. Broderick and Levinson have no financial relationships to disclose.

Dr. Berinstein is a committee member of the Ophthalmic Mutual Insurance Company and a stockholder in Covalent Medical LLC.

patient and checking the consent form.

This often occurs again in the OR prior to draping and is finally verified in the standard “time-out” before starting the procedure. While some of these checks and verifications can be mirrored in the clinic for most in-office procedures, certain differences render clinic procedures more vulnerable to adverse events.

Retina clinic vs. OR

A standard retina practice in the United States is often a busy, fluid and evolving environment that may predispose retina specialists or their staff to committing errors. As opposed to the OR, where the focus of the care team is typically on only one patient in one room at a time, a provider in a retina clinic may see in excess of 50 patients on an average day spread over multiple rooms that are in constant turnover. Furthermore, the physician in the clinic also faces a multitude of distractions—phone calls, texts and staff interruptions.

Medical practices face unique challenges in managing and training employees. They require a management infrastructure with proper oversight to promote standardized training methods, define employee responsibilities and maintain retention of experienced staff. Office-based care may also involve a larger care team concomitantly managing multiple patients, potentially from multiple providers, at the same time. It’s essential the care team communicate and maintain a healthy teamwork climate to ensure safety.

The nature of the procedures performed in the retina clinic, specifically intravitreal injections, can lead to potential error and WSPEs. The physician’s treatment algorithm for injections can depend on the disease being treated, type of medication and patient factors, as well as insurance guidelines. These factors may result in a multitude of treatment plans involving simultaneous treatment of both eyes or sequential treatment at different times. A large quantity of injectable medications are



A sheet of labeled stickers to be placed over the treated eye. “A” indicates Avastin, “E” Eylea, “L” Lucentis, “O” Ozurdex and “T” triamcinolone.

often stocked and freely accessed in a fast-paced environment.

In OR-based settings, especially in hospitals, medications are often taken from a centralized, controlled system (i.e., BD Pyxis MedStation). In such systems, the patient name and medication must be verified and entered into the electronic system in order to obtain the medication. Subsequent barcode scanning of patient bracelets and medications are required before administering the medication. Such automated systems are generally not available in the clinic.

EHR and the potential for WSPEs

Medical records can become a source of WSPEs starting with the initial clinic encounter. A recent study found that “upstream” errors in the form of erroneous lens specifications or calculations originating in the clinic may be responsible for up to a quarter of WSPEs in ORs. These errors would not have been necessarily prevented by conducting a time-out in the OR.⁶ Many electronic health record systems use drop-down windows or checkbox functions that can inadvertently lead the user to select the

A standard retina practice in the United States is often a busy, fluid and evolving environment that may predispose retina specialists or their staff to committing errors.

A typical procedure checklist

1. Obtain consent for procedure.
2. Mark the eye(s) with sticker.
3. Confirm procedure plan and location with patient at time of sticker placement.
4. For injections, the technician confirms procedure site and medication with patient at time of prep.
5. The physician confirms with patient the eye(s) and medication with patient upon re-entering room.
6. Final time out immediately before procedure begins (laser or injection).

In many instances, the EHR uses drop-down windows or checkbox functions that can inadvertently lead the user to select the wrong eye or medication in clinic notes.

wrong eye or medication in clinic notes.

Many EHRs have a carry-forward function that allows the provider to transfer previously documented exam notes to notate a current patient encounter. This can be useful to expedite vast amounts of required documentation, but it can cause problems if the information being carried forward is dated or inaccurate.

Upon entering the room, the physician or staff member must closely confirm on the computer monitor that the medical record and images are for the correct patient. Following the exam, the doctor needs to diligently review the notes for accuracy before finalizing them.

Tools for reducing preventable errors

Procedural checklists have evolved over the years in an attempt to reduce the risk of potential wrong site surgery. The Joint Commission introduced the well-known Universal Protocol in 2004, which has been adopted and implemented in ORs across the United States. In 2012, the Ophthalmic Mutual Insurance Company invited the American Academy of Ophthalmology and other key organizations to help develop an ophthalmic-specific surgical checklist (available at <https://www.omic.com/ophthalmic-surgical-checklist/>).

In 2014, the AAO subsequently developed additional recommendations to minimize preventable surgical site and procedure errors.⁷ Many of these recommendations are specifically focused on inpatient or ambulatory surgical centers. However, limited consensus or guidelines

on clinic-specific protocols exist for office-based retina procedures. Standardized safety protocols used in the OR should be modified and implemented in office-based settings, keeping in mind the key differences already noted.

Our office protocol

In our practice, we have developed a standardized clinical protocol for in-office procedures to address safety concerns and potentially reduce the risk of WSPEs (*box*). Our protocol begins when the physician and patient agree on a treatment plan. Before each procedure, the informed consent is either obtained or reviewed. This provides an opportunity to confirm the eye (or eyes in the case of a bilateral treatment plan) and medication. With the scribe present, the physician will then place a sticker over the eye or eyes. The sticker has a large capital letter indicating the name of the medication (A for Avastin, E for Eylea, etc., *Figure, page 29*).

Before prepping the eye, the technician again confirms the treatment with the patient as they review the consent form together. The physician, who may have evaluated or treated other patients in the meantime, will then re-enter the room and once again confirm the patient, site and medication before proceeding with the treatment.

We use this general protocol for other office procedures, such as lasers and pneumatic retinopexy. These repeat checks and confirmations at multiple stages of the process reduce the risk of error with in-office procedures without adding significant time to the process. Having the patient and other team members participate in the site and medication confirmation reduces reliance on memory and helps the retina specialist better deal with the workload, complexity and stressors of a busy retina practice. The medication-specific sticker serves as a visual reminder that creates shared situational awareness amongst all team members.

(Continued on page 43)



Super View HTC Lens Hassan-Tornambe Contact Lens



- **Maximum stability**
Due to unique and innovative design
- **Always sterile**
Disposable design minimizes risk of infection and cross-contamination
- **Perfect view in every case**
Guarantees the greatest depth of field in every surgery

Visit our booth 2029 during AAO, San Francisco.

www.oculussurgical.com +49 641 2005-298




 Follow us! 855-SDI-BIOM (Toll Free, US Only)


OCULUS[®]
SURGICAL

How ultra-widefield imaging is changing our view of DR

The state of the science of how novel UWFI systems are improving our ability to observe diabetic changes in the peripheral retina.



Sana Idrees, MD



Rajeev Ramchandran, MD, MBA



Ajay E. Kuriyan, MD, MS

By Sana Idrees, MD, Rajeev Ramchandran, MD, MBA, and Ajay E. Kuriyan, MD, MS

Take-home points

- » Diabetic retinopathy-related changes can lead to irreversible vision loss, making early detection of disease essential.
- » Ultra-widefield imaging is capable of capturing 200-degree images of the retina.
- » Studies have demonstrated that UWFI can capture additional peripheral diabetic retinopathy pathology that would otherwise be missed if examination was limited to the posterior pole.
- » Research is underway to understand the importance of peripheral lesions in diabetic retinopathy grading and management.

Early detection of diabetic retinopathy is essential to prevent vision loss, and annual eye exams are recommended for surveillance of diabetic patients. Vision changes secondary to DR can be irreversible. Identification of prognostic markers in the peripheral retina may be essential to guiding management and reducing the disease burden earlier in the disease course. Novel ultra-widefield imaging systems are greatly enhancing our ability to observe diabetic changes in the peripheral retina.

Here, we review the state of the science of ultra-widefield imaging in monitoring and managing diabetic retinopathy.

Improving upon ETDRS standard

Back in 1991 the Early Treatment Diabetic Retinopathy Study established the standard seven-field image as the gold standard for detection and classification of DR.¹ While montage images have been found to be reliable for the assessment of

DR, they're time-consuming to acquire and require a skilled photographer and pharmacologic pupil dilation. Conventional fluorescein angiography utilizes retinal photography that can view 30 to 50 degrees of the retina at any given time.² However, this field of view excludes much of the peripheral retina.

UWFI systems can generate high-resolution images with up to 200-degree (82 percent) views of the retina with scanning laser ophthalmoscopy. UWFI includes options for color photos, red-free images, fundus autofluorescence, and fluorescein and indocyanine green angiography.^{3,4}

Concordance between standard images and UWFI

Several studies have examined concordance in the detection of DR between reference standard images and UWFI. Similar concordance in DR detection has been established between dilated fundus examination, standard seven-field images

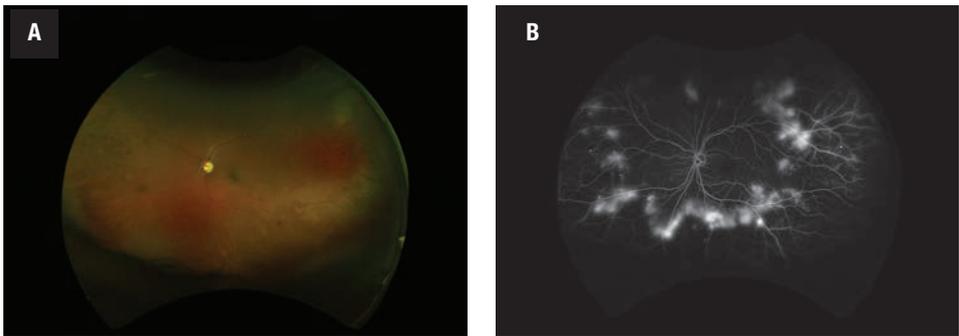


Figure 1. Ultra-widefield fundus photograph (A) and fluorescein angiogram (B) demonstrating non-high-risk proliferative diabetic retinopathy with peripheral non-perfusion.

and UWFI.⁴⁻⁸ However, agreement between DR severity grades in dilated fundus examination or reference standard images and UWFI has been variable.

Visualization of the peripheral retina with UWFI allows the detection of more peripheral lesions and has been demonstrated to lead to higher DR severity grading compared to grading based upon standard seven-field imaging.^{9,10} UWFI has also been shown to detect more proliferative DR and severe nonproliferative DR than clinical exam alone.⁶

Significance of predominantly peripheral lesions

Predominantly peripheral lesions (PPLs) have been defined as DR lesions with a greater extent of the lesions outside vs. inside the standard seven ETDRS fields. A comparison between eyes with and without PPLs as identified on UWFI demon-

strated that eyes with PPLs had a 3.2-fold increased risk of two-step or more DR progression on the ETDRS DR severity scale and a 4.7-fold increased risk of progression to PDR (Figure 1).¹¹ Two retrospective case series reported that approximately 10 percent of DR cases presented with lesions only outside of the standard seven fields.^{9,12}

Peripheral retinal non-perfusion in DR stimulates the production of vascular endothelial growth factor, leading to a breakdown of the blood-retinal barrier and development of diabetic macular edema and neovascularization (Figure 2).^{13,14} Ultra-widefield angiography has been shown to detect approximately four times more retinal non-perfusion and two times more neovascularization compared to conventional standard seven-field imaging (Figure 3, page 34). Additionally, UWFA detected non-perfusion and neovascularization in 10 percent of eyes that would

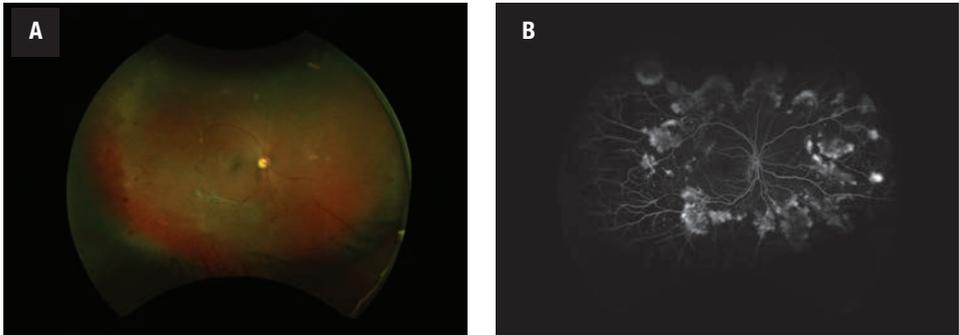


Figure 2. Ultra-widefield fundus photograph (A) and fluorescein angiogram (B) demonstrating non-high-risk proliferative diabetic retinopathy with extensive peripheral neovascularization and significant non-perfusion, especially in the temporal periphery.

Bios
 Dr. Idrees is a vitreo-retinal surgery fellow at the Flaum Eye Institute, University of Rochester (N.Y.) Medical Center, where Dr. Ramchandran is an associate professor and Dr. Kuriyan an assistant professor.

DISCLOSURES: Drs. Idrees and Ramchandran have no relationships to disclose.

Dr. Kuriyan is a consultant for Alimera Sciences, Bausch Health, Regeneron, and Roche/Genentech, and receives grant funding from Second Sight and Roche/Genentech.

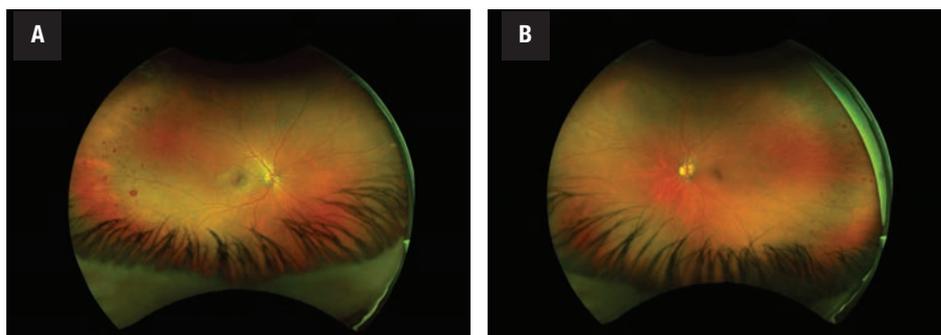


Figure 3. Ultra-widefield fundus photographs demonstrating non-high-risk proliferative diabetic retinopathy in the right (A) and left (B) eye with intraretinal hemorrhages largely found in the peripheral retina and focal area of neovascularization in the superotemporal macula.

As a screening tool for diabetic retinopathy, fundus photography is especially useful in geographic areas where access to an ophthalmologist is limited.

have otherwise been missed by standard FA (Figure 4).⁹

Reports of the association between peripheral non-perfusion and DME are conflicting. Some studies have reported a significant correlation between DME and peripheral retinal ischemia on UWFI. Matthew Wessel, MD, and colleagues found that eyes with retinal ischemia had 3.75-times increased odds of having macular edema compared to those without retinal ischemia.¹³

Similarly, Ravi Patel, MD, and colleagues reported a correlation between recalcitrant DME with larger areas of retinal non-perfusion in UWFA and greater severity of DR.¹⁴ In contrast, Paolo Silva, MD, and colleagues didn't find an association between clinically significant macular edema and the area of non-perfusion.¹¹

Potential of nonmydriatic UWFI

As a screening tool for DR, fundus photography is especially useful in geographic areas where access to an ophthalmologist is limited. A large study comparing nonmydriatic fundus photos to nonmydriatic

UWFI showed that UWFI reduced the number of ungradable eyes by 81 percent, increased the identification of DR by nearly twofold and identified peripheral lesions suggesting more severe DR in approximately 10 percent of patients.¹⁵ These findings suggest that UWFI is a convenient and practical tool that can provide high-quality images for reliable diabetic retinopathy screening.

One major advantage of these imaging systems is that they can capture ultra-wide-field images without pupil dilation, which is beneficial in diabetic patients who may have a poor response to mydriatic agents.¹⁶

Nonmydriatic UWF color images were compared to mydriatic UWF color images and were found to have exact agreement in DR grading in 96.8 percent of cases.⁵ Additionally, UWFI can be achieved with single-field photography, which allows for shorter imaging time and greater comfort for the patient.

Nonmydriatic UWFI for fundus photography was compared to standard nine-field imaging acquired after pupil dilation. The results showed that DR severity grading

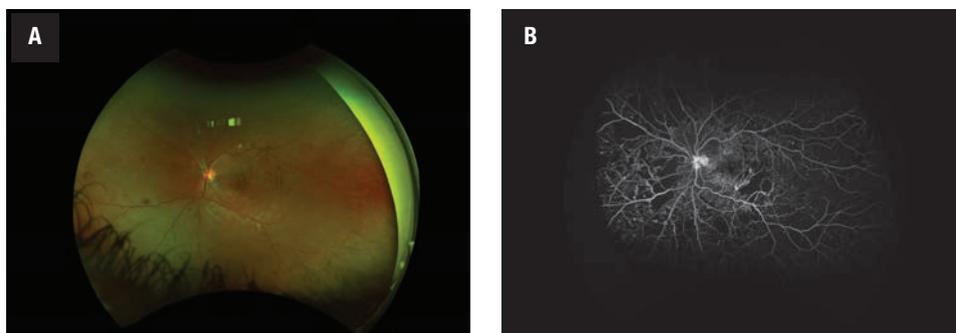


Figure 4. Ultra-widefield fundus photograph (A) and fluorescein angiogram (B) demonstrating high-risk proliferative diabetic retinopathy with extensive neovascularization of the disc and peripheral nonperfusion..

was similar between the two systems, and concluded that UWFI was fast and effective, making it acceptable for mass screening for diabetic retinopathy.¹⁷

Emerging imaging platforms

New treatment modalities, such as targeted retinal photocoagulation (TRP), are being explored for the treatment of DME and neovascularization. TRP involves selective application of laser to areas of non-perfusion as detected by FA to reduce the level of vascular endothelial growth factor produced by ischemic retina.¹⁵ Mahiul M.K. Muqit, PhD, FRCOphth, and colleagues evaluated the effect of UWF FA-guided TRP in 28 eyes with proliferative DA, finding disease regression in 76 percent of eyes at 12 weeks and complete regression in 37 percent at 24 weeks.¹⁸

The same group compared TRP, minimally traumatic panretinal photocoagulation (MT-PRP) and standard-intensity panretinal photocoagulation (SI-PRP) and found that, while all three groups had similar rates of PDR regression, the TRP and MT-PRP groups had significant reductions in central retinal thickness.¹⁹ UWF FA allows for improved identification of specific areas of retinal non-perfusion to assist in techniques, such as TRP.

Bottom line

The use of UWFI in screening for DR has been widely studied, and its utility is well-established. There is now a growing body of evidence that suggests that UWFI is of considerable importance in the diagnosis, grading and management of DR. Research has established a similar concordance between reference standard images and UWFI with regard to rate of DR detected.

In terms of diabetic severity grading, UWFI has demonstrated high agreement with standard seven-field imaging and improved detection of proliferative and severe non-proliferative DR compared to dilated fundus examination. UWFI has a clear ad-

vantage over reference standard images with regard to documenting peripheral lesions. The importance of these peripheral lesions is still under investigation.

New treatment approaches based on UWFI technology are being studied. Large-scale clinical studies investigating UWFI are underway and may further shape our understanding of the role of UWFI technology in diabetic retinopathy. 

REFERENCES

1. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airle House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98(Suppl):786-806.
2. Ghasemi Falavarjani K, Tsui I, Satta SR. Ultra-wide-field imaging in diabetic retinopathy. *Vision Res*. 2017;139:187-190.
3. Shoughy SS, Arevalo JF, Kozak I. Update on wide- and ultra-widefield retinal imaging. *Indian J Ophthalmol*. 2015;63:575-581.
4. Kernt M, Hadi I, Pinter F, et al. Assessment of diabetic retinopathy using nonmydriatic ultra-widefield scanning laser ophthalmoscopy (Optomap) compared with ETDRS 7-field stereo photography. *Diabetes Care*. 2012;35:2459-2463.
5. Rasmussen ML, Broe R, Frydkjaer-Olsen U, et al. Comparison between Early Treatment Diabetic Retinopathy Study 7-field retinal photos and non-mydriatic, mydriatic and mydriatic steered widefield scanning laser ophthalmoscopy for assessment of diabetic retinopathy. *J Diabetes Complications*. 2015;29:99-104.
6. Manjunath V, Papastavrou V, Steel DHW, et al. Wide-field imaging and OCT vs clinical evaluation of patients referred from diabetic retinopathy screening. *Eye Lond Engl*. 2015;29:416-423.
7. Silva PS, Cavallerano JD, Sun JK, Soliman AZ, Aiello LM, Aiello LP. Peripheral lesions identified by mydriatic ultrawide field imaging: Distribution and potential impact on diabetic retinopathy severity. *Ophthalmology*. 2013;120(12):2587-2595.
8. Silva PS, Cavallerano JD, Sun JK, Noble J, Aiello LM, Aiello LP. Nonmydriatic ultrawide field retinal imaging compared with dilated standard 7-field 35-mm photography and retinal specialist examination for evaluation of diabetic retinopathy. *Am J Ophthalmol*. 2012;154:549-559.
9. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. *Retina*. 2012;32:785-791.
10. Price LD, Au S, Chong NV. Optomap ultrawide field imaging identifies additional retinal abnormalities in patients with diabetic retinopathy. *Clin Ophthalmol Auckl NZ*. 2015;9:527-531.
11. Silva PS, Cavallerano JD, Haddad NMN, et al. Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 Years. *Ophthalmology*. 2015;122:949-956.
12. Bae K, Lee JY, Kim TH, et al. Anterior diabetic retinopathy studied by ultra-widefield angiography. *Korean J Ophthalmol KJO*. 2016;30:344-351.
13. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. *Br J Ophthalmol*. 2012;96:694-698.
14. Patel RD, Messner LV, Teitelbaum B, Michel KA, Hariprasad SM. Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. *Am J Ophthalmol*. 2013;155:1038-1044.
15. Silva PS, Horton MB, Clary D, et al. Identification of diabetic retinopathy and ungradable image rate with ultrawide field imaging in a national teleophthalmology program. *Ophthalmology*. 2016;123:1360-1367.
16. Huber MJ, Smith SA, Smith SE. Mydriatic drugs for diabetic patients. *Br J Ophthalmol*. 1985;69:425-427.
17. Mathis T, Lereuil T, Bruneteau L, et al. [Performance of ultra-wide field retinophotography for screening of diabetic retinopathy]. *J Fr Ophtalmol*. 2019;42:572-578.
18. Muqit MMK, Marcellino GR, Henson DB, et al. Optos-guided pattern scan laser (Pascal)-targeted retinal photocoagulation in proliferative diabetic retinopathy. *Acta Ophthalmol*. 2013;91:251-258.
19. Muqit MMK, Young LB, McKenzie R, et al. Pilot randomized clinical trial of Pascal TargETED Retinal versus variable fluence PANretinal 20 ms laser in diabetic retinopathy: PETER PAN study. *Br J Ophthalmol*. 2013;97:220-227.

In terms of diabetic severity grading, UWFI has shown high agreement with standard seven-field imaging and improved detection of proliferative and severe non-proliferative DR.

Report from ASRS 2019

Downside of finger flicks, upside of abicipar changes

These findings and three other presentations on SRF/IRF, stable CST and oral therapy give new insights into nAMD.



Ashkan M. Abbey, MD

By Ashkan M. Abbey, MD

Take-home points

- » A small amount of subretinal fluid with active anti-VEGF treatment may be optimal for long-term vision improvement.
- » HAWK/HARRIER data suggest prioritizing treatments would minimize fluctuations of central subfield thickness.
- » An oral small-molecule antagonist of human CCR3 was found to be safe and well tolerated.
- » A higher risk of release of silicone oil droplets occurred with most currently used syringes, and the risk increases significantly with agitation.
- » MAPLE demonstrated an improved safety profile for abicipar pegol after modification of its manufacturing process.

The annual meeting of the American Society of Retina Specialists in Chicago showcased the latest in diagnostics, treatment and management strategies for retinal disease. The meeting once again demonstrated how rapidly the field of retina is advancing.

Here, we present summaries of five of the most intriguing presentations, primarily related to neovascular age-related macular degeneration. They include an analysis of the relationship between residual fluid on optical coherence tomography and vision outcomes, the effects of fluctuations in retinal thickness on vision outcomes, an investigative oral therapy for nAMD, the increased risk of silicone oil release after agitation of syringes used for intravitreal injections and the safety of abicipar pegol following a modified manufacturing process.

Intraretinal and subretinal fluid and associated vision outcomes

This year's meeting highlighted the ongoing debate regarding the need for aggressive treatment of fluid on OCT in patients with nAMD. Nancy Holekamp, MD, aimed to provide better understanding of the impact of residual fluid on vision outcomes by performing a retrospective review of 917 treatment-naïve nAMD patients from the HARBOR trial. All patients were treated with ranibizumab (Lucentis, Roche/Genentech) on a monthly or as-needed basis.¹

In this cohort, fewer than 30 percent of eyes had residual subretinal (SRF) or intraretinal fluid (IRF) after 12 and 24 months of treatment. In the SRF group, the mean residual SRF thickness was 90.6 μm at 12 months and 82.6 μm at 24 months. Interestingly, eyes with residual SRF had significantly greater improvements in best-corrected visual acuity from baseline than eyes

Bio

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

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

with resolved SRF. The odds of attaining 20/40 or better BCVA were similar for eyes with or without SRF.

Eyes with residual IRF had significantly less improvement in BCVA compared to eyes with resolved IRF. The odds of attaining 20/40 or better BCVA were lower for eyes with residual IRF when compared to eyes with resolved IRF.

Eyes with residual SRF (no IRF) only experienced the greatest gain in BCVA and achieved the highest BCVA letter scores at 12 and 24 months. Vision outcomes were similar among eyes with resolved or residual SRF and IRF. Eyes with only residual IRF (no SRF) had the worst outcomes.

“It’s the treating, not the drying, that’s needed for good vision outcomes,” Dr. Holekamp concluded.

The take home: This study brings into question the need to completely dry all SRF on OCT in nAMD patients. A small amount of SRF on OCT with active anti-VEGF treatment appears to be optimal for long-term vision improvement.

Dr. Holekamp disclosed relationships with Allergan, Genentech, Novartis and Regeneron Pharmaceuticals.

HAWK, HARRIER: CST fluctuations lead to worse visual outcomes

The HAWK and HARRIER Phase III randomized clinical trials compared brodalumab 3 or 6 mg (Novartis) to aflibercept 2 mg (Eylea, Regeneron Pharmaceuticals) therapy for nAMD. All patients received three monthly loading doses for three months. Brodalumab patients were then given treatment every 12 weeks, and the treatment interval could be reduced to every eight weeks based upon disease activity. Aflibercept patients were treated every eight weeks after the three loading doses.

This analysis divided HAWK and HARRIER patients into quartiles based upon the standard deviation of each eye’s central subfield thickness (CST) from baseline to week 96.² The standard deviation was to be used as a metric of individual CST



Finger flicking a syringe before intravitreal injections may not be a good idea. See page 38.

variability. The 444-patient quartiles were divided by SD as follows:

- <27 μm (no fluctuation in CST after completion of loading phase).
- 27-44 μm (dry after loading phase with minor fluctuations in CST).
- 44-68 μm (moderate fluctuations in CST).
- 68 μm (marked fluctuations in CST).

Using the first quartile (minimal CST fluctuation) as the reference, the study found that increasing variability in CST was associated with worse BCVA outcomes at week 96. Mean BCVA change at 96 weeks was 10.3 letters for quartile 1, 8.8 letters for quartile 2, 6.9 letters for quartile 3, and 2.1 letters for quartile 4. The latter quartile had a mean gain of 8 letters less than quartile 1.

The study concluded that maintaining stable CST translates into better disease control and superior visual outcomes in nAMD. Furthermore, a more stable CST was associated with a dry retina.

The take home: Based upon this data, retina specialists should prioritize the use of treatments that will minimize fluctuations of CST to achieve the best visual outcomes in nAMD.

Presenter Chirag D. Jhaveri, MD, disclosed relationships with the Diabetic

Findings from the HARBOR cohort call into question the need to completely dry all sub-retinal fluid on optical coherence tomography in patients with neovascular age-related macular degeneration.

We should carefully consider the type of syringe our compounding pharmacy is using in order to avoid this potential complication, and avoid agitation of the syringe.

Retinopathy Clinical Research Network, Genentech, Novartis and Regeneron.

Finger-flicked syringes release SO droplets at higher rates

The 2018 ASRS Practices and Trends survey found that 5.2 percent of retina specialists in the United States have performed a vitrectomy for symptomatic vitreous floaters due to silicone oil (SO) droplets following intravitreal injections of bevacizumab.³ This study assessed the release of SO by eight different models of syringe tested in multiple *in vitro* conditions. A separate, related study examined the frequency of SO droplets apparent at clinical examination.

Masked graders performed all analyses using light microscopy. The presence of silicone oil was confirmed by Fourier-transform infrared spectroscopy. Of the eight different commonly used syringe models tested, the Braun Injekt-F oil-free syringe was the only one not found to release SO. Of note, with all syringes tested, agitation of the syringe (analogous to “flicking” with one’s finger) led to a statistically significant increase in the amount of SO released.

In the clinical study, 37 eyes undergoing routine intravitreal injections of bevacizumab were compared with 30 control eyes and evaluated with slit-lamp examination and ultrasonography to assess the amount of SO in the vitreous. Slit-lamp examination found SO in the vitreous in 68 percent of treated eyes and ultrasound found SO in 76 percent. The amount of silicone oil was correlated with the number of prior injections.

This study identifies a higher risk of release of SO droplets with most of the currently utilized syringes. The risk increases significantly with agitation.

The take home: We should carefully consider the type of syringe that our compounding pharmacy uses in order to avoid this potential complication, and avoid agitation of the syringe.

Presenter Gustavo Barreto de Melo, MD, PhD, had no relevant financial relationships to disclose.

Oral therapy for nAMD

Not all patients achieve adequate anatomic and/or visual improvements when regularly receiving intravitreal injections of anti-VEGF for nAMD. This study evaluated an oral therapy for nAMD patients refractory to standard anti-VEGF therapy.⁴

C-C chemokine receptor type 3 (CCR3) and its ligand CCL11 are highly expressed in subretinal neovascular lesions. Inhibition of CCR3 disrupts endothelial cell migration, which reduces the morphological changes associated with pathologic choroidal neovascularization. AKST4290 (Alkahest) is an orally administered small-molecule antagonist of human CCR3.

In this Phase IIa, single-arm, open-label study, 24 nAMD patients unresponsive to IVT anti-VEGF therapy (i.e., persistent fluid and no BCVA improvement after at least three monthly injections) were given AKST4290 oral monotherapy for six weeks. Seventy-two percent had stable or improved BCVA, and the mean improvement in BCVA was 2 letters. Eight percent of subjects gained ≥ 10 letters. CST did not change significantly during the six weeks of treatment, but then improved significantly in the subsequent four weeks of follow-up without treatment. The study found AKST4290 to be safe and well-tolerated.

In a related Phase IIa study in treatment-naïve nAMD eyes, BCVA improved in 83 percent of eyes with a mean gain of 7 letters.

The take home: Effective oral therapy for nAMD would be a welcome addition to our treatment armamentarium that could reduce the need for myriad IVT injections and their associated risks and costs.

Presenter Michael W. Stewart, MD, disclosed relationships with Alkahest, Allgan and Regeneron.

MAPLE: Abicipar safety improved following manufacturing changes

Abicipar pegol (Allergan), a DARPin-binding protein, is a pegylated recombinant ankyrin protein that binds all isoforms of

KEEP UP WITH EVERYTHING RETINA BY KEEPING UP WITH RETINA SPECIALIST

VEGF-A with high affinity and specificity. It has been shown *in vitro* to bind to VEGF-A with a significantly higher affinity than ranibizumab.

The CEDAR and SEQUOIA Phase III trials found abicipar given every eight or 12 weeks at fixed dosing was non-inferior to ranibizumab monthly dosing in treatment-naïve nAMD patients. Visual acuity gains were similar across in all three arms of the study. However, these studies noted an increased incidence of intraocular inflammation (IOI) in patients receiving abicipar.

The MAPLE study was designed to evaluate the safety and treatment effect of abicipar manufactured with a modified process to optimize the removal of host-derived impurities.⁵ The 28-week study included both treatment-naïve nAMD patients and those who had previous anti-VEGF treatments. Three loading doses followed by two doses eight weeks apart were administered in 123 patients.

The overall incidence of IOI was 8.9 percent, down from 13.1 percent and 13.8 percent in CEDAR and SEQUOIA, respectively. Most events were assessed to be mild to moderate. Severe events of IOI were reported in 1.6 percent of patients (vs. 3.4 and 3 percent in CEDAR and SEQUOIA), all of which resolved with topical and/or oral corticosteroids. There were no reported cases of endophthalmitis or retinal vasculitis.

The take home: CEDAR and SEQUOIA demonstrated the potential of abicipar to reduce treatment burden in nAMD. However, many were alarmed by the elevated IOI rates. The MAPLE study helps to alleviate those concerns by demonstrating an improved safety profile after a modified manufacturing process. The Food and Drug Administration recently accepted a biologics license application for abicipar, bringing us one step closer to a promising new treatment option for nAMD.

Presenter Raj K. Maturi, MD, disclosed relationships with Aerpio, Allegro, Allergan, Genentech and Graybug Vision. 

REFERENCES

1. Holekamp NM, Ghanekar AA, Hill L, Yang M, Gune S. What do the HARBOR data reveal about the relationship between the drying of subretinal and intraretinal fluid and associated vision outcomes? Presented at American Society of Retina Specialists 37th annual scientific meeting; July 27, 2019; Chicago, IL.
2. Jhaveri CD, Dugel PU, Wykoff CC, et al. 96-week visual and expanded anatomical outcomes of brodalumab versus aflibercept in patients with nAMD: Results from HAWK and HARRIER. Presented at ASRS 37th annual scientific meeting; July 27, 2019; Chicago, IL.
3. De Melo GB, Emerson GG, Dias Jr. C, et al. Silicone droplets are released by syringes and found in the vitreous. Presented at ASRS 37th annual scientific meeting; July 27, 2019; Chicago, IL.
4. Stewart MW, Jeffords E, Klutzaritz V, Rawner E, Newman E. Open-label study evaluating the effects of the CCR3 antagonist ALK4290 in patients with neovascular AMD refractory to anti-VEGF therapy. Presented at ASRS 37th annual scientific meeting; July 27, 2019; Chicago, IL.
5. Maturi RK. Abicipar Phase 2 MAPLE trial supports improved safety for patients with nAMD following a modified manufacturing process. Presented at ASRS 37th annual scientific meeting; July 30, 2019; Chicago, IL.



THREE WAYS TO DO IT:

1

Go to our website @
www.retina-specialist.com

2

Follow us on Twitter
@RetSpecMag

3

Like us on Facebook @
RetinaSpecialistMag

Secure your tech and stay compliant

A security risk analysis can protect your data—and you're supposed to do it anyway.

By **Larry K. Neiswender**



Department Editor
Kari Rasmussen

Bios

Ms. Rasmussen is chief operating officer of Rocky Mountain Retina Consultants, Salt Lake City.

Mr. Neiswender is managing partner, Microsoft certified systems administrator and practice workflow and health information technology redesign specialist for Protect EHR LLC, North Richland Hills, Texas, and at www.protectehr.com. His company performs security risk analyses, which are discussed in this article.

Ransomware and Data Destruction Attacks Dominate Healthcare Threat Landscape (HIPAA Journal, June 11, 2019)

This is a headline from just one of hundreds of articles I've collected over the last eight years and is proof of what all of us should be willing to accept: As an industry, retina specialists are a prime target for individuals and organizations with no moral compass.

I have well over 30 years' experience in information technology but gave up selling or performing any kind of IT service when I saw, firsthand, how practices were struggling to understand this previously unexperienced environment. This background allows me to help practices understand where they're vulnerable technically. The problem is, one of the most prevalent problem isn't usually technical, and that has been a truth since the beginning of electronic patient data.

The three flavors of data threats

Here are two more headlines to ponder: *OCR – Healthcare Organizations Unaware of Privacy Regulations (Fierce Health IT, April 26, 2013)*

Study Reveals Healthcare Industry Employees Struggling to Understand Data Security Risks (HIPAA Journal, April 30, 2018)

These articles came five years apart, but there's apparently a very consistent problem. Here's what health-care attorney Marla Hirsch said in her 2016 article for Fierce Healthcare:¹ "What's even more concerning is that inside employees were responsible for more than half of November's breaches, a notable increase from past months." Another article noted that repeat offenders caused 30 percent of health-care data breaches in the second

quarter of 2018.² *Tech Republic* reported earlier this year that employee errors are a larger threat to data security than hackers or insiders.³

So, while this makes it seem that the greatest problem is at the employee level, it's important to remember that threats come in three flavors: administrative; physical; and technical. So is there anything a practice can use to get a handle on where it may be exposed to threats?

Security risk analysis

The SRA first appeared in the HIPAA Security Rule, but because this was six years before the introduction of Meaningful Use, there was little fanfare regarding the required process. Even worse was the fact that many believed it only related to practices participating in Medicare and Medicaid. The simple truth is, if an entity creates, maintains, transmits or receives confidential patient information in any electronic format, HIPAA requires it to have an SRA.

When an SRA is conducted the way the Office of the National Coordinator for Health Information Technology intended, this requirement is a simple two-step process that addresses all three of the areas described above, posing questions that help the practice to determine its current footprint related to security and compliance regarding patient data. And yet, the failure to perform the SRA has been a leading cause of HIPAA violations since 2012.

In 2011, the first year of meaningful use, Congress ordered an audit of participating practices to determine the program's efficacy. Congress authorized 150 audits, but the process stopped at 115 because the audits had already disclosed 980 HIPAA violations. The most prevalent violation was the failure to have the



SRA performed. Today, in an overwhelming majority of cases where penalties are assessed by the Department of Health and Human Services, one of the failures is not having performed the SRA. One medical imaging company paid a \$3 million settlement for exposing more than 300,000 patient health records. One of the violations HHS cited was a failure to conduct a risk analysis.⁴

Three things an SRA evaluates

Space won't allow me to go into depth on the SRA, but here are things that every practice can afford to do in regard to the three essential elements, and the SRA evaluates all of them:

- **Obtain a personalized policies and procedures manual.** Don't be foolish and buy templates off of the internet. You are expected to have policies that directly reflect the way you run your practice. Generalized policies will do nothing but back you into an indefensible corner. Then, make sure every one of your employees reads the manual. (How can you expect them to help you protect the practice if they don't understand the responsibilities you're required to meet?)
- **Make sure all your employees get training.** This should not only address HIPAA, but also introduce employees to phishing and other forms of malware attacks. Use a program that tests them

afterward, and don't accept the kind of test a 4-year old could guess at and pass.

- **A true firewall is the single most important piece of tech you can own.** They're not that expensive, but don't accept the device your internet provider installs and tells you "this is your firewall/router, so you're protected."

I'm a golf buff—not any good, but I love the game—but if you've ever learned anything about the game you would have heard the name Ben Hogan. He said something that is only 10 words long and each word only has two letters, but I can't think of anything that rings truer for each of us in this industry today: "If it is to be – it is up to me."

A good place to start is with the SRA. Learn from it and grow from there. 

REFERENCES

1. Hirsch M. 2016 a Banner year for EHR security breaches. Fierce Healthcare. December 29, 2016. Available at: <https://www.fiercehealthcare.com/it/feature-2016-banner-year-for-ehr-security-breaches>
2. Davis J. 142 healthcare data breaches in Q2, 30% caused by repeat offenders. Healthcare IT News. August 9, 2018. Available at: <https://www.healthcareitnews.com/news/142-healthcare-data-breaches-q2-30-caused-repeat-offenders>
3. Sanders J. Employee mistakes and system errors are a larger threat to data security than hackers or insiders" TechRepublic. March 26, 2019. Available at: <https://www.techrepublic.com/article/employee-mistakes-and-system-errors-are-a-larger-threat-to-data-security-than-hackers-or-insiders/>
4. Press release: Tennessee diagnostic medical imaging services company pays \$3,000,000 to settle breach exposing over 300,000 patients' protected health information. Department of Health and Human Services; Washington, DC. May 6, 2019. Available at: <https://www.hhs.gov/about/news/2019/05/06/tennessee-diagnostic-medical-imaging-services-company-pays-3000000-settle-breach.html>

A true firewall is the most important piece of tech you can own. They're not that expensive, but don't accept the device your internet provider installs.

Step therapy: Where do we stand?

Answers to questions that linger since Medicare Advantage organizations started implementation for anti-VEGF treatments.



By **Ellen R. Adams, MBA**



Have a question for
“Coding Commentary”?
Tweet it to us
[@RetSpecMag](https://twitter.com/RetSpecMag)

Bio

Ms. Adams is a consultant with Corcoran Consulting Group. She can be reached at 1-800-399-6565 or at www.corcoranccg.com.

In August 2018, the Centers for Medicare and Medicaid Services announced plans to institute step therapy for some Medicare beneficiaries enrolled in Medicare replacement plans, also known as Medicare Advantage plans.¹ Historically, step therapy was only used to control costs within private insurance plans. CMS touted this step therapy rule as a cost-saving measure with little downside to most patients.¹

Since Medicare Advantage organizations now cover more than 30 percent of Medicare-eligible beneficiaries, with increased market penetration expected in the future,² it behooves a physician to understand the CMS rules affecting this population of patients to avoid costly claim denials.

Step therapy requires a physician to initially use a “step 1” drug to treat a disease for qualifying beneficiaries. “Step 1” drugs are “cost-effective,” sometimes generic or biosimilar drugs. Step therapy treatments require that the patient demonstrate step 1 treatment failure, also known as “fail first,” before the physician can propose and apply for prior-approval to use a more expensive treatment. Ophthalmologists may encounter step therapy when treating certain patients with ranibizumab (Lucentis, Roche/Genentech) or aflibercept (Eylea, Regeneron). Some Medicare Advantage organizations (MAOs) now require step therapy for neovascular age-related macular degeneration, diabetic macular edema, macular edema from retinal vein occlusion, choroidal neovascularization or radiation retinopathy macular edema.

Exceptions to step therapy

But there are exceptions to the step therapy requirement. Patients who started treatment prior to the rule’s implementation on January 1 this year will not be forced to switch from ranibizumab or aflibercept to bevacizumab; the policy only applies

to treatment-naïve patients. Beneficiaries not properly notified by the MAO of the step therapy provision in their policies are likewise not obliged to follow it. Patients with allergies or medical contraindications to bevacizumab, or inability to tolerate the side effects of bevacizumab, may also seek exception to step therapy.

However, the exceptions don’t automatically entitle the patient access to alternative drugs. If the physician believes the patient qualifies for an exception, he or she must apply for an expedited exemption, to which the MAO must reply “as expeditiously as the beneficiary’s condition requires.”¹ CMS expects that most MAOs will respond to an expedited request within 72 hours.

Once started on step therapy, if the patient and/or physician doesn’t believe that bevacizumab is providing an adequate treatment response, then the MAO’s prior authorization process should be followed to “step up” to ranibizumab or aflibercept.

What does ‘ineffective’ mean?

How is *ineffective therapy* with bevacizumab defined? The answer isn’t very clear as yet, but one approach employs the Food and Drug Administration-approved directions for use as a starting point. The prescribing information for aflibercept for wet AMD is 2 mg (0.05 mL) administered by intravitreal injection every four weeks (approximately every 28 days/monthly) for the first three months, followed by the same dose every eight weeks (two months). For ranibizumab, the prescribing information is 0.5 mg (0.05 mL) once a month (approximately 28 days); it directs that patients may be treated with three monthly doses followed by less frequent dosing with regular assessment.

It’s clear the prescribing information recommends no treatment change until the three loading doses are administered

and the patient is evaluated for a therapeutic response. With this perspective, it would take three injections of bevacizumab, at a minimum, to gather sufficient information to demonstrate failure of step therapy.

Some MAOs could deny the request for a “step up.” Anticipating this possibility, the physician needs clear chart documentation of treatment failure that can be submitted for prior approval or appeal of a rejection. This might include serial optical coherence tomography scans showing persistent subretinal fluid, serial OCT showing lack of consistent anatomic improvement, eye examination documentation showing vision impairment secondary to persistent sub- or intraretinal fluid, or fluorescein angiography showing lack of reduction of leakage of the neovascularized area. If the patient is an active self-advocate, they may be directed by the MAO to contact the physician to submit an appeal; the patient does not have access to submitting an appeal on their own behalf.³

The MAOs serving the states of Idaho, Montana and Oregon require evidence of proven failure after three bevacizumab treatments or a loss “greater than 15 letters of visual acuity.”⁴ Physicians who object to step therapy are asked by some MAOs to refer the patient to a physician who will comply.

Sharing the savings

CMS’ press release announcing step therapy in mid-2018 described shared savings for patients accordingly:¹

Part B step therapy requirements may reduce costs for both the beneficiaries and MA plans. MA plans will be required to pass savings on to beneficiaries through the rewards furnished as part of the drug

management care coordination program. Rewards passed on to the patient will be required to be equivalent to more than half the amount saved on average per participant.

A number of organizations have stated their opposition to step therapy. They include Prevent Blindness, in cooperation with the American Academy of Ophthalmology and the American Society of Retina Specialists. Their position is that “CMS lacks the authority to permit its Medicare Advantage plans to impose such a coverage tool.”⁵

On the other hand, America’s Health Insurance Plans, the trade group representing commercial payers and which has blamed drug companies for high pharmaceutical costs, has been pleased with it. In response to criticism from patient advocacy groups, CMS Administrator Seema Verma said, “There were protections built in to prevent patients from losing access to medications.”⁶ Despite the controversy, you need to understand how step therapy functions to address this issue when it arises. 

REFERENCES

1. Medicare Advantage prior authorization and step therapy for Part B drugs [press release]. Baltimore, MD; Center for Medicare and Medicaid Services. August 7, 2018. <https://www.cms.gov/newsroom/fact-sheets/medicare-advantage-prior-authorization-and-step-therapy-part-b-drugs> Accessed September 7, 2019.
2. Japsen B. Humana’s enrollment of seniors in Medicare Advantage eclipses 3M. Forbes. May 2, 2018. <https://www.forbes.com/sites/brucejapsen/2018/05/02/humanas-enrollment-of-seniors-in-medicare-advantage-eclipses-3m/#4553a0ad600f> Accessed September 7, 2019.
3. How does step therapy work? Blue Cross/Blue Shield Blue Care Network of Michigan. <https://www.bcbsm.com/index/health-insurance-help/faqs/plan-types/pharmacy/what-is-step-therapy.html> Accessed September 7, 2019.
4. American Academy of Ophthalmology. Congress’ physicians prep strong message opposing step therapy in Medicare. June 27, 2019. <https://www.aao.org/eye-on-advocacy-article/congress-physicians-prep-strong-message-opposing> Accessed September 7, 2019.
5. Prevent Blindness. Coalition seeks patient stories regarding step therapy and prior authorization. <https://www.preventblindness.org/patient-step-therapy-stories> Accessed September 7, 2019.
6. Inserro A. CMS aims at drug prices through Part D, MA step therapy, pharmacy rebates. Am J Man Care. November 27, 2018. <https://www.ajmc.com/newsroom/cms-aims-at-drug-prices-through-part-d-ma-step-therapy-pharmacy-rebates> Accessed September 7, 2019.

Strategies to reduce errors

(Continued from page 30)

Bottom line

We don’t fully know the true scope of preventable WSPEs in the office setting, because significant underreporting may exist. These errors have the potential to cause harm to the patient’s ocular health. Even if no concrete harm occurs, these situations can be deleterious to the physician-patient relationship.

Errors still occur amongst high-functioning, conscientious and efficient teams due to the numerous factors that can negatively impact individual and team situational awareness in fast-paced clinics. Instituting a clear and established protocol for in-office procedures can help minimize the risk of harm. 

Anne M. Menke, RN, PhD, patient safety manager for the Ophthalmic Mutual Insurance Company, provided input in the preparation of this article.

REFERENCES

1. U.S. Department of Health and Human Services; Agency for Healthcare Research and Quality Patient Safety Network. Wrong-site, wrong-procedure, and wrong-patient surgery. <https://psnet.ahrq.gov/primer/18/wrong-site-wrong-procedure-and-wrong-patient-surgery>. Updated January 2019. Accessed September 11, 2019.
2. Ambe PC, Sommer B, Zirngibl H. Wrong site surgery: Incidence, risk factors and prevention. Chirurg. 2015;86:1034-1040.
3. Hempel S, Maggard-Gibbons M, Nguyen DK, et al. Wrong-site surgery, retained surgical items, and surgical fires: A systematic review of Surgical never events. JAMA Surg. 2015;150:796-805.
4. Seiden SC, Barach P. Wrong-site/wrong-site, wrong-procedure, and wrong-patient adverse events: Are they preventable? Arch Surg. 2006;141:931-939.
5. Neily J, Mills PD, Eldridge N, et al. Incorrect surgical procedures within and outside of the operating room: A follow-up report. Arch Surg. 2011;146:1235-1239.
6. Parikh R, Palmer V, Kumar A, Simon JW. Surgical confusions in ophthalmology: Description, analysis and prevention of errors from 2006-2017. Ophthalmology. Article in Press. <https://doi.org/10.1016/j.ophtha.2019.07.013> Accessed August 15, 2019.
7. American Academy of Ophthalmology. Recommendations of AAO Wrong-Site Task Force—2014. <https://www.aao.org/patient-safety-statement/recommendations-of-american-academy-ophthalmology>. Updated August 2014. Accessed August 13, 2019.

Twitter as a ‘microblog’

It's a good place to start promoting your practice online, but know the pearls and pitfalls of online content creation.



Department Editor
David R.P. Almeida,
MD, MBA, PhD

The most common question I'm asked is, "Now that I have my website running and created my social media profiles, where do I start promoting my practice?" In my opinion, Twitter is the logical starting point for any physician or practice. Think of Twitter as your "microblog." Your tweets allow you to highlight your brand and connect with colleagues, patients and others in an easily digestible and enjoyable form. Tweets, which are 280 characters or less, don't require significant energy and time inputs.

Importantly, anyone can read Tweets. Although only registered users can post Tweets and comments, anyone with an internet connection can view your Tweets. Thus, patients without Twitter accounts can still access your professional and practice message.

Moreover, a record of all Tweets is stored on your home page which offers a summary of your practice. Whereas practice websites tend to be more formalized in structure and content, patients typically enjoy a person's Twitter profile because it provides text, images and videos that they may find more relevant to their interests. As you grow your Twitter presence, this will be reflected in your Twitter homepage. I recommend adding web links from your Twitter account to your practice website and vice versa to facilitate easy user navigation.

What do you post?

So, what do you post on your new Twitter "microblog"? Going back to some of the fundamentals we reviewed in the first two columns, you should strive to provide value consistent with the brand you are trying to affirm. Careless posts (e.g., what you ate for breakfast) are going to dilute your overall Twitter message. Instead, look to create posts that provide information of value to potential readers. Your microblog will ideal-

ly be a resource for patients and colleagues.

Look to communicate interesting cases, medical updates, novel research, conference attendance and continuing medical education. These will hopefully have some inherent value to patients, colleagues and others reading your Twitter feed.

Pearls and pitfalls

There are a couple of pitfalls I commonly see when physicians start to post content. First, and by far the most important, is that you may not provide specific patient information online. This violates patient privacy and has legal consequences.

Do not, under any circumstance, use an online platform to communicate directly with a patient about a specific medical problem. In cases where a patient may want to communicate, I recommend you or your office contact that patient directly by phone and move the discussion to a private phone call or an in-office visit.

Similarly, any interesting case you post should be anonymized with the removal of any possible identifying information. You may also want to ask the patient if they are agreeable to you posting the case. What you are trying to avoid here is having the patient come across your Twitter feed, recognize your case posting as their own, and being upset that they were not informed of this.

Second, be careful with advertising or promoting products or services on your posts. Although it's acceptable to post any sales or events specific to your practice, you do not want to extend this to third-party companies. This has the potential for conflicts of interest, which can damage patient-physician and patient-practice relationships. This returns to our point of ensuring your Twitter feed is consistent with your brand and practice objectives.

Good luck. I look forward to seeing what you tweet. 

Bio

Dr. Almeida is in private practice at Erie Retinal Surgery in Erie, Pa.

DISCLOSURE: Dr. Almeida reports no relevant financial relationships.

• Twitter:
@davidalmeidamd

• Email: drpa@pm.me

Closing the escape route of anti-VEGF-A

By suppressing VEGF-C and -D, OPT-302 shows potential to improve outcomes in nAMD with existing therapies.

By **Richard Mark Kirkner**



Department Editor Emmett T. Cunningham Jr., MD, PhD

Opthea describes OPT-302 as a biologic acting as a “trap” that blocks VEGF-C and -D from binding the receptors VEGFR-2 and -3, whereas existing anti-VEGF agents target VEGFR-1 and -2.

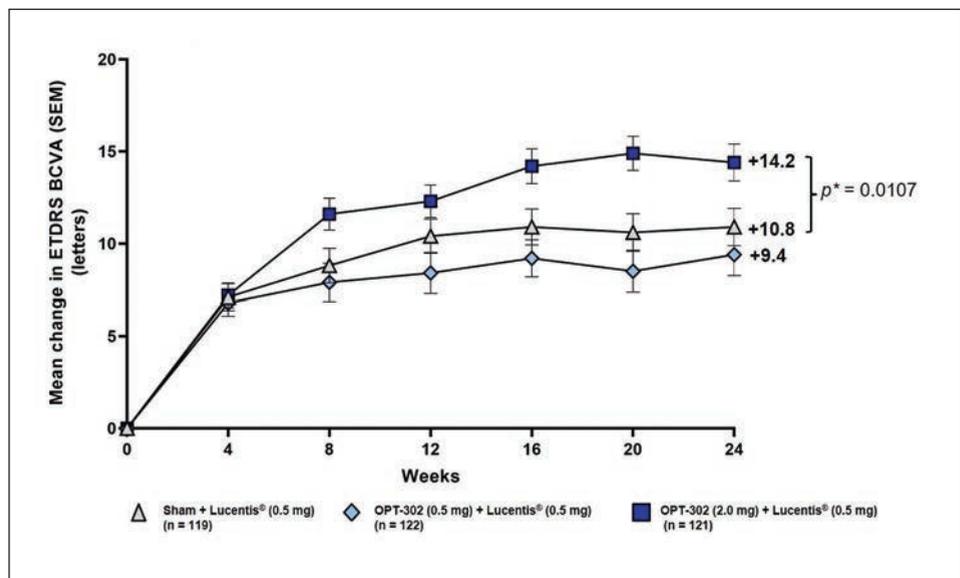
At the Ophthalmology Innovation Summit at the American Society of Retina Specialists meeting in July, Opthea CEO and managing director Megan Baldwin, PhD, said that topline data from the Phase IIb trial of OPT-302 in neovascular age-related macular degeneration would report out in the third quarter. Precisely 12 days later, it did.

Where the three dominant anti-VEGF medications target vascular endothelial growth factor A, OPT-302 targets VEGF-C and -D (aflibercept [Eylea, Regeneron], additionally targets VEGF-B and placental growth factor). Inhibition of VEGF-A upregulates VEGF-C and -D. Opthea describes OPT-302 as a novel biologic acting as a “trap” that blocks VEGF-C and -D from binding to the receptors VEGFR-2 and -3, whereas the existing anti-VEGF agents target receptors VEGFR-1 and -2.

The Phase IIb trial in nAMD is evaluating combination therapy of two different doses of OPT-302—2 and 0.5 mg—in combination with 0.5-mg ranibizumab (Lucentis, Roche/Genentech) vs. 0.5-mg ranibizumab alone. Patients receive monthly treatments. Twenty-four-week results have shown the higher-dose combination group gained 14.2 letters of vision on average vs. a 10.8-letter gain for the monotherapy group, a statistically significant difference ($p=0.0107$). The 0.5-mg OPT-302 group showed a gain of 9.4 letters.

The higher-dose and monotherapy groups showed consistent reductions in central subfield thickness—a reduction of 147 μm from 414 μm at baseline in the former, and a reduction of 134 μm from 413 μm in the latter.

OPT-302 is also the subject of a Phase IIa trial in combination with aflibercept in diabetic macular edema, the first read-



Graph shows mean gains and standard error of the mean (SEM) in Early Treatment Diabetic Retinopathy Study best-corrected visual acuity from baseline to 24 weeks of three different dosing arms in the OPT-302 Phase IIb trial.

out of which is due early next year. Going forward, Opthea anticipates presenting more data from the Phase IIb study in nAMD at upcoming conferences and topline data from the Phase IIa trial in DME in early 2020, Dr. Baldwin said.

Here, Pravin U. Dugel, MD, of Retinal Consultants of Arizona, provides insight into the Phase IIb trial. Dr. Dugel is an investigator on the trial and serves as a consultant to Opthea.

Q Describe the mechanism of action of OPT-302 in your own words.

A The science behind OPT-302 comes from oncology, where it's well established that when VEGF-A is suppressed, redundant pathways upregulate VEGF-C and -D and might provide a sort of escape mechanism. The thinking is that suppressing VEGF-A, -C and -D simultaneously, or pan-VEGF suppression, can eliminate the redundant pathways and provide better clinical outcomes.

Q How did the earlier trials inform the Phase IIb trial?

A The early phase studies in nAMD included a monotherapy arm not because the company was going to take monotherapy to market, but to show that the product was actually producing a biological signal. The safety profile in all these trials was excellent, and there was clearly a biological signal, including in the monotherapy arm. What was most impressive was that in 50 percent of patients in the combination therapy arm, the neovascular membrane wasn't detectable as read by the central independent reading center. Clearly, these results warrant further clinical trials.

Q How would you summarize the key finding of the Phase IIb trial?

A It showed what we expected, which is that OPT-302 has an excellent safety profile and a definite biological signal. Also, the 2-mg combination dosing showed statistically significant superiority to Lucentis monotherapy, even when the control arm performed exceptionally well. That was very encouraging because it follows the expected science. I think it deserves to move to a Phase III trial.

Q How can this change the treatment of nAMD?

A When I think of what the opportunity is for the treatment of nAMD, I think of three different silos: immediate or early improvement in efficacy; increased durability; and maintenance of vision over the long term. If we can achieve all three that would be phenomenal. But, at this point even achieving only one would be a very valuable drug indeed. A Phase III trial will provide the scientific scrutiny to determine where it fits in this schema. Regardless, given the recent results, this drug has much potential and deserves to proceed to Phase III.

OPT-302 has the potential to provide a complementary pathway. The science is established in oncology. Much of what we know in chronic retinal disease is extrapolated from oncology, so it gives us more confidence when the clinical results follow the science.

Q What are the next steps in the development of OPT-302?

A More data analysis needs to be done—scientific presentations, publications—but certainly it's not the end, it's just the very beginning. There's also data from the DME study that's still pending readout. ^{RS}

DISCLOSURES: Dr. Dugel is a consultant to Opthea.

The science behind OPT-302 comes from oncology, where it's well established that when VEGF-A is suppressed, redundant pathways upregulate VEGF-C and -D and might provide a sort of escape mechanism.

OUTPERFORM CONVENTIONAL.

Conventional Slit Lamp Imaging



Fundus Module 300 Slit Lamp Attachment



THE FUNDUS MODULE 300 SLIT LAMP ATTACHMENT: Make superior fundus imaging part of the regular slit lamp exam.

Conventional slit lamp imaging requires that you have a separate fundus camera to capture the range and depth of non-mydratiac retina imaging. But the Fundus Module 300 from Haag-Streit is a slit lamp attachment that brings fundus imaging into the regular slit lamp examination.

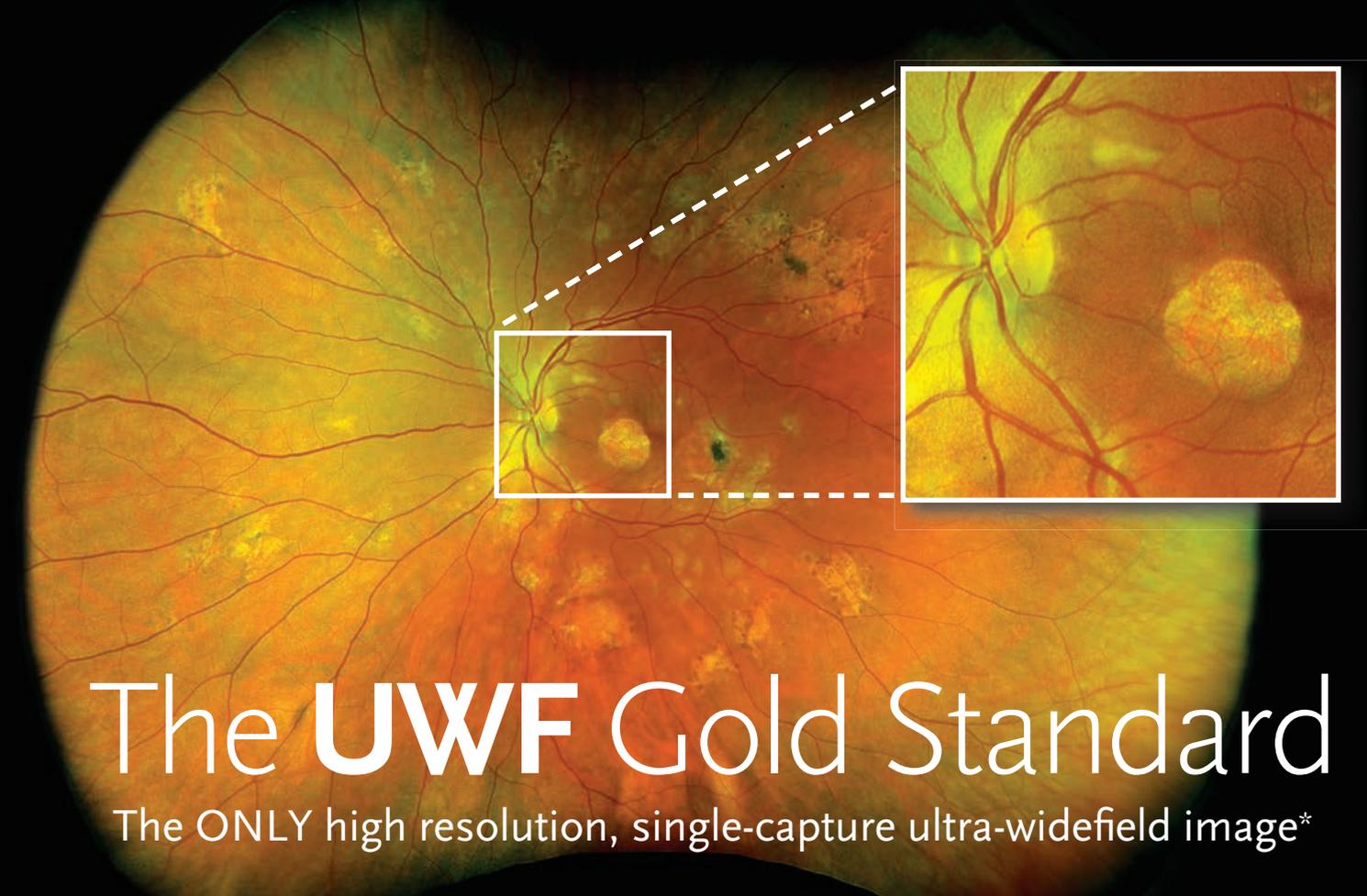
The image quality of the Fundus Module 300 by far exceeds the conventional possibilities on slit lamps – it even stands up to comparison with full-blown screening fundus cameras. It's time to fall in love with advanced fundus imaging that's efficient, and designed to allow you to capture images during the retinal exam.

Are you ready to outperform conventional? Learn more about how Haag-Streit is driven to excellence. Visit [HSDriven.com/fundus](https://www.hsdriven.com/fundus).

800.787.5426

© 2019 Haag-Streit USA. All Rights Reserved.

 **HAAG-STREIT**
USA



The **UWF** Gold Standard

The **ONLY** high resolution, single-capture ultra-widefield image*



- ✓ 200° retinal coverage
- ✓ high-resolution detail
- ✓ patient-friendly, minimal flash
- ✓ single-capture, no sweeps

optomap GOLD STANDARD UWF is the only system that covers vortex ampullae in all 4 quadrants in a single-capture.* UWF imaging in less than ½ second.

Visit Optos at AAO Booth # S-127

Find out more at www.optos.com

Contact us to put **optomap** in your practice,

call **800-854-3039** or email **BDS@optos.com**

