A PUBLICATION BY REVIEW of Ophthalmology

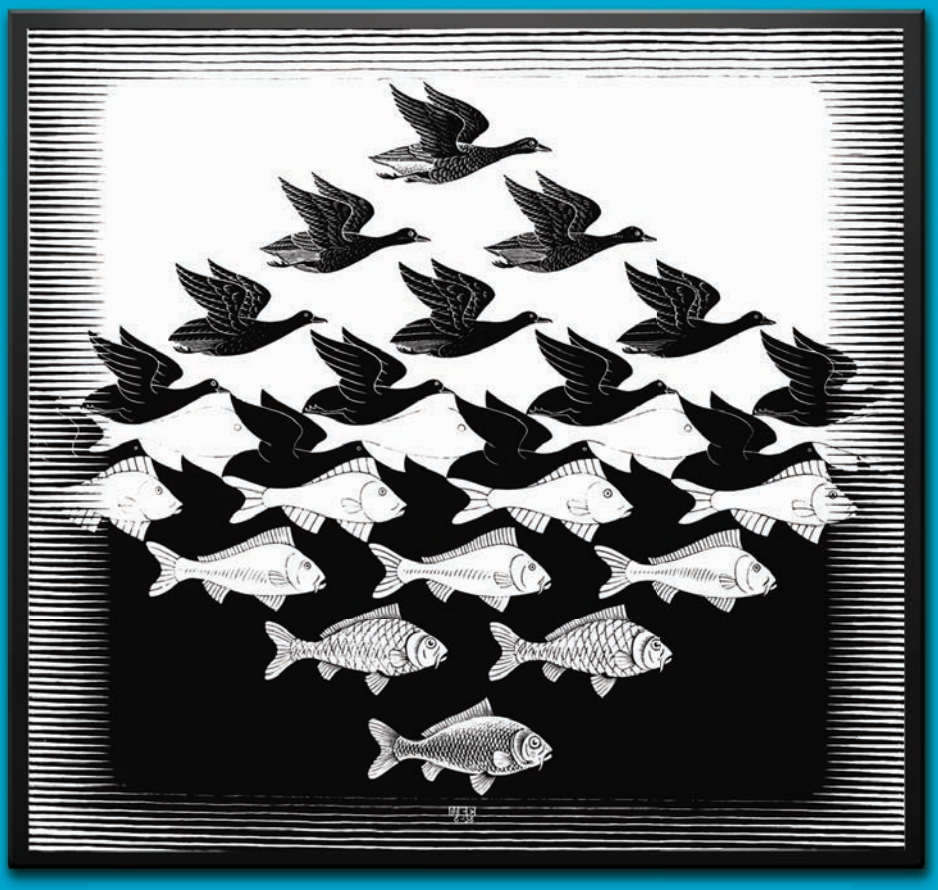
RETINA SPECIALIST

MARCH 2015

LESSONS FROM DRCR.NET PROTOCOL T

What we can take from the study.

PAGE 18



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

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

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

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

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

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

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

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

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

Adverse Reactions
Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous

UPDATED DME INDICATION

SEE DME Differently.

- **The pathophysiology**
  — An **inflammatory cascade** plays a key role[1-5]
- **The therapeutic targets**
  — Suppress multiple **inflammatory cytokines**[6]
- **The clinical results**
  — Achieve clinically significant **3-line gains** in BCVA[6,*]

Now for use in the general DME population

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

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

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

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

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

*Best-corrected visual acuity.

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

1. Jain A, Varshney N, Smith C. The evolving treatment options for diabetic macular edema. *Int J Inflam.* 2013;2013:689276. **2.** Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol.* 2009;54(1):1-32. **3.** Ehrlich R, Harris A, Ciulla TA, Kheradiya N, Winston DM, Wirostko B. Diabetic macular oedema: physical, physiological and molecular factors contribute to this pathological process. *Acta Ophthalmol.* 2010;88(3):279-291. **4.** Scholl S, Kirchhof J, Augustin AJ. Pathophysiology of macular edema. *Ophthalmologica.* 2010;224(suppl 1):8-15. **5.** Zhang W, Liu H, Al-Shabrawey M, Caldwell RW, Caldwell RB. Inflammation and diabetic retinal microvascular complications. *J Cardiovasc Dis Res.* 2011;2(2):96-103. **6.** OZURDEX® Prescribing Information.

ALLERGAN Retina

www.Ozurdex.com APC52TE14 143433

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

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

INDICATIONS AND USAGE

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

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

Diabetic Macular Edema

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

CONTRAINDICATIONS

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

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

Retinal Vein Occlusion and Posterior Segment Uveitis

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

Adverse Reactions Reported by Greater than 2% of Patients

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

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

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

Diabetic Macular Edema

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

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

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

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

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

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

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

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

Cataracts and Cataract Surgery

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with OZURDEX® is low. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test. Adequate fertility studies have not been conducted in animals.

PATIENT COUNSELING INFORMATION

Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects

Advise patients that in the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

IN BRIEF

• **Genentech** received Food and Drug Administration approval for **Lucentis** (ranibizumab injection) for treatment of diabetic retinopathy in diabetic macular edema. The FDA in February granted Lucentis Breakthrough Therapy Designation and Priority Review for this indication based on results from the RISE and RIDE Phase III clinical trials.

• **RXi Pharmaceuticals Corp.** has received a U.S. patent for the delivery of double-stranded siRNAs (21 to 23 nucleotides in length) across the blood-retina barrier for the treatment of wet age-related macular degeneration or diabetic retinopathy. The patent, part of RXi's acquired OPKO estate, is scheduled to expire in 2023.

• **Spark Therapeutics** has initiated enrollment of a Phase I/II clinical trial of its product candidate, SPK-CHM, for patients with choroideremia.

• **Allegro Ophthalmics** received a $2 million grant from the Type 1 Diabetes Program of The Leona M. and Harry B. Helmsley Charitable Trust to support a Phase II study of **Luminate**, its integrin peptide therapy currently in multiple Phase II studies, for treatment of diabetic macular edema.

• **iCura Vision** has licensed the intellectual property portfolio and associated research and development program for an oral medication intended to treat dry AMD. The company intends to place the first of these candidates, ICR-14967, into clinical development in 2016. Under the terms of the licensing agreement, the **National Institute of Health's Blueprint Neurotherapeutics Network**, which has funded the discovery and early development of the medication, will continue to provide financial support through Phase I studies.

Sunshine Act Review Period Set to Open

You may have already received a notice from the Centers for Medicare and Medicaid Services (CMS) to register for the Open Payments system. Come April, individual physicians will have an opportunity to view payment data CMS has collected from device makers and pharmaceutical companies before the information goes public.

The release is part of the Open Payments program, also known as the Physician Payment Sunshine Act, created by the Affordable Care Act. It will list consulting fees, research grants, travel reimbursements and other gifts medical device makers, drug companies and group purchasing organizations paid physicians and teaching hospitals for all of 2014. The initial release last year included only data for the last five months of 2013.

The 2013 data listed 4.4 million payments totaling nearly $3.5 billion. Some 1,419 manufacturers and group purchasing plans paid that out to 546,000 individual physicians and 1,360 teaching hospitals. The 2013 data omitted another $1.1 billion in payments because of data problems.

Last year only 26,000 physicians, or 4.8 percent, registered in the Open Payments system to review the payments attributed to them.

The American Academy of Ophthalmology (AAO) is encouraging members to review the data before the June 30 release. "Members who might have erroneous data reported in their name ought to be proactive in identifying and correcting that," says Michael X. Repka, MD, AAO medical director for government affairs. "If I was going to tell an ophthalmologist what to do, I would say sign up, take advantage of the period of time in which data are there for review to identify disputed data, as CMS calls it, and request its withdrawal."

Eli Y. Adashi, MD, MS, a professor at Brown University in Providence, R.I., explored the problems with the initial data release in a recent article in the *Journal of the American Medical Association*.[1] "Last year was different," he says in an interview. "There really wasn't all that much time. The website was clunky and, worse, it failed and had to be taken off line for close to two weeks."

Dr. Adashi has advised physicians who receive significant commercial support to take advantage of the review and dispute period. "The key argument in looking at the data is to ensure accuracy, but not just in dollar amounts, but the breakdown of support into categories to see that they're appropriately characterized," he says.

"This is not a once and done pro-

cess; it's an ongoing process for our members," Dr. Repka says. "Even though the public wasn't much interested last year in the data, it doesn't mean they won't be this time."

Registration is available on the CMS website at cms.gov/OpenPayments/Program-Participants/Physicians-and-Teaching-Hospitals/Registration.html.

REFERENCE

1. Santhakumar S, Adashi EY. Viewpoint: The Physician Payment Sunshine Act; Testing the value of transparency. JAMA. 2015;313:23-24.

DARPin Abicipar Pegol a 'Free Call Option' for Actavis

Actavis PLC is awaiting results from a key clinical trial before it decides the next step with Allergan's most promising anti-age related macular degeneration (AMD) therapy, DARPin abicipar pegol.

Actavis CEO and President Brent Saunders told a Goldman Sachs conference in January that DARPin abicipar pegol "is not in our model." He called the drug "kind of almost like a free call option," and noted it has the potential generate billions in revenue. "And I think the question of how much we invest in it will really be a decision we take after we see the Japanese study readout in the second quarter," Mr. Saunders said.

That was a reference to the BAMBOO trial (NCT02101504), a Phase II study in Tokyo currently recruiting patients. The trial is comparing the safety and efficacy of abicipar pegol to ranibizumab (Lucentis, Genentech) and a sham in patients with wet AMD over 20 weeks total. The study is due to be completed in August.

Allergan licensed the DARPin platform—it stands for designed ankyrin repeat proteins—from Molecular Partners AG in Switzerland.

Molecular Partners last year released results from the Allergan-sponsored, double-masked stage 3 Phase II study that demonstrated that DARPin abicipar pegol provided equal or potentially higher vision gains for wet AMD with fewer injections compared to existing anti-VEGF therapy. At the time, Allergan announced that full Phase III development would start in the second quarter this year.

Mr. Saunders said one issue with abicipar pegol has been "a little inflammation, which is not a surprise," and that other anti-VEGF drugs had similar issues until they were reformulated. A reformulation has shown promise in rabbit eyes, he said.

"The Japanese study will really confirm that for us, but if we have a drug that can be dosed three, four times a year, well then we've got a game-changer," he said. That would also give Actavis, soon to be renamed Allergan, a multi-billion-dollar drug that would "fuel a lot of future growth," Mr. Saunders said.

But in the meantime, he said the company would concentrate on combinations and other drugs.

Overall, the combined company announced it would invest more than $1 billion in brand product development this year. Actavis Senior Vice President C. David Nicholson, PhD, will become executive vice president for branded research and development and report to Mr. Saunders. RS

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
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL:
REVOPHTHALMOLOGY@CAMBEYWEST.COM

CIRCULATION
PO BOX 71, CONGERS, NY 10920-0071
(877) 529-1746
OUTSIDE USA: (845) 267-3065

SENIOR CIRCULATION MANAGER
HAMILTON MAHER
(212) 219-7870 hmaher@jhihealth.com

CHIEF OPERATING OFFICER
JEFF MACDONALD

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, HUMAN RESOURCES
LORRAINE ORLANDO

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

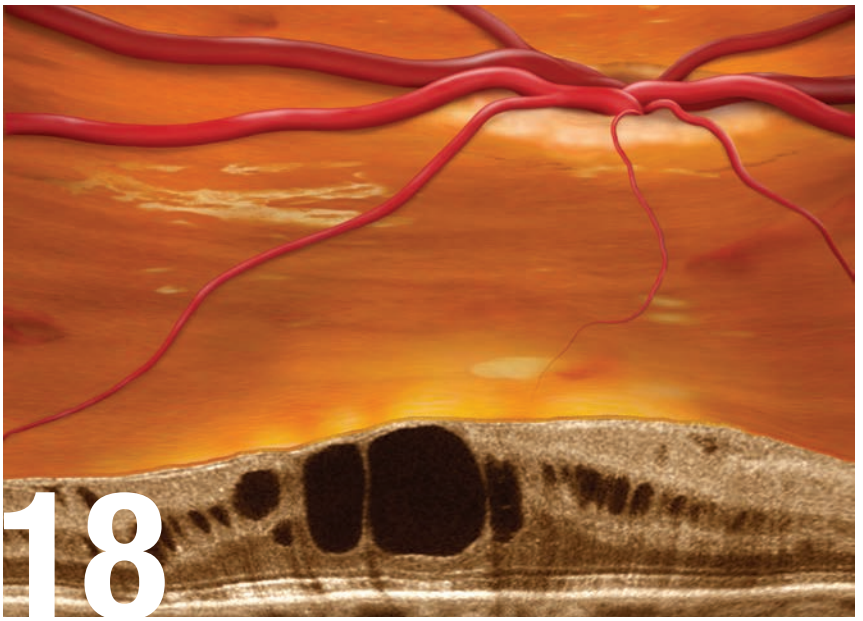
VICE PRESIDENT, CIRCULATION
EMELDA BAREA

jmi

100 Avenue of the Americas
New York, NY 10013

A PUBLICATION BY REVIEW

RETINA SPECIALIST



18

MARCH 2015

FEATURES

DEPARTMENTS

Cover art by Mark Erickson
jiredesign.com

OUR SCIENCE. YOUR ART. THEIR VISION.

As Demonstrated in 2 Pivotal, Phase 3 Trials in Patients With DME Evaluating Mean Change in BCVA* at 52 Weeks vs Baseline[1]

EYLEA® (aflibercept) Injection Offers Extended Dosing in DME—2-mg Every 8 Weeks Following 5 Initial Monthly Doses[1]

Initial Dosing	Follow-Up Dosing
5 Initial 2-mg Injections Monthly (Every 4 Weeks)	2-mg Every 2 Months (Every 8 Weeks)

Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

*BCVA = best-corrected visual acuity, as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.
- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies during the first year was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.
- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

IMPORTANT PRESCRIBING INFORMATION FOR EYLEA® (aflibercept) INJECTION

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

For more information, visit www.EYLEA.com.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. October 2014.

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

1/2015
LEA-0687

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Adverse Reactions	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%
Eye pain	9%	6%
Cataract	8%	9%
Vitreous floaters	6%	3%
Corneal erosion	5%	3%
Intraocular pressure increased	5%	3%
Conjunctival hyperemia	5%	6%
Vitreous detachment	3%	3%
Foreign body sensation in eyes	3%	3%
Lacrimation increased	3%	2%
Vision blurred	2%	2%
Intraocular inflammation	2%	<1%
Injection site pain	2%	<1%

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

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

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-52 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

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

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

U.S. License Number 1760

Issue Date: October 2014
Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents

LEA-0618

A PUBLICATION BY RP REVIEW
RETINA SPECIALIST

11 Campus Blvd., Suite 100
Newtown Square, PA 19073
Telephone (610) 492-1000
Fax (610) 492-1049

Editorial inquiries (610) 492-1003
Advertising inquiries (610) 492-1011
E-mail rccl@jobson.com

Jobson Medical Information LLC

By Charles C. Wykoff, MD, PhD

Welcome and Hang On!

"The only thing that is constant is change." — Heraclitus, 535 B.C.

When I was born, there were 4 billion people on Earth. Today, 75 percent more people are bustling about our planet—over 7 billion, with a cresting gray tsunami and a life expectancy in the United States of 79 years. The majority of retinal diseases afflict adults, increasing in prevalence with age; these exudative and degenerative disorders result in far more blindness in developed countries than all other eye diseases combined.

Fortunately, the developments of treatments for many of these afflictions are shifting the epidemiology of visual impairment. Incident cases of age-related macular degeneration-derived blindness have fallen 50 percent in some developed countries since the dawn of the anti-VEGF revolution.

The management of exudative retinal diseases was initially fairly straightforward: *To inject or not to inject*? Maybe throw in, *To add laser or not to add laser*?

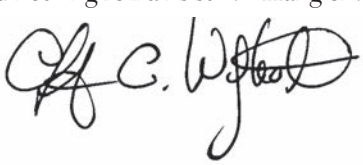
But, with accumulating comparison data (*DRCR.net Protocol T, page 18*) coupled with an expanding list of pharmacologic agents (*steroid implants, page 30*), the decision tree for managing retinal diseases is growing ever more complex.

As of March 1, Clinicaltrials.gov listed 2,395 "retina" studies, including 659 actively recruiting. Over the next decade, the debates of bevacizumab versus aflibercept versus ranibizumab will be but one of many important conversations with clinical, economic and—May I add?—possibly ethical implications.

For the retina specialist, pharmacologic agents are but one of the issues to consider; choices of diagnostic equipment, laser devices and surgical instrumentation are expanding even more rapidly.

Over the months and years to come, *Retina Specialist* will strive to be a unique, doctor-mediated forum for vitreoretinal specialists across the United States and around the globe to stay informed on the latest approaches, technologies and trials impacting the care of our patients as well as our evolving practice management environment.

While the Greek philosopher Heraclitus may have lived over 2,500 years ago, when the human population was just 1 percent what is it today, his teachings are more relevant than ever: "All entities move and nothing remains still." Hang on!



By E. Radhika Ramenaden, MD, and Philip J. Rosenfeld, MD, PhD »

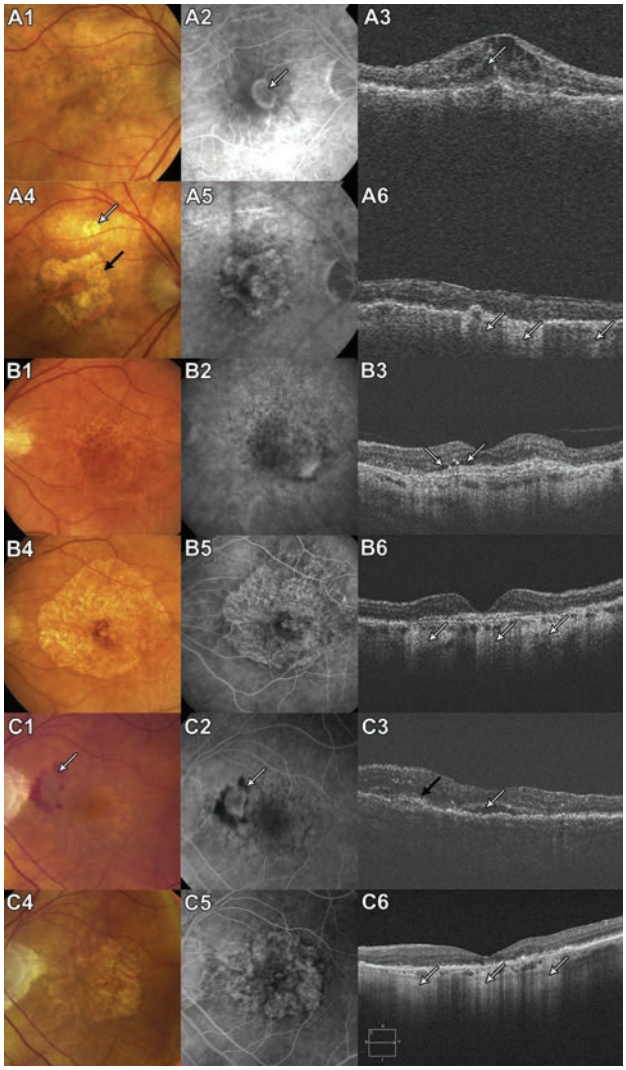
Can Anti-VEGF Cause GA in Wet AMD?

A host of trials are trying to answer this question. Here's what they've found so far.

There is no doubt that anti-VEGF therapy is the gold standard for the treatment of macular neovascularization (MNV) in AMD.[1-5] In the Phase III ANCHOR and MARINA trials, monthly intravitreal injections of ranibizumab (Lucentis, Genentech) resulted in overall vision improvement with 90 percent of eyes losing fewer than 15 letters of vision at two years.[1,2,6]

When we analyzed the subjects in these two studies who lost or gained at least three lines of vision after two years, we found that the color fundus, fluorescein angiographic (FA) and optical coherence tomography (OCT) images from eyes with vision loss showed dry lesions without fluorescein leakage characterized as atrophic scars. At that time, we proposed that vision loss after anti-VEGF was unlike vision loss associated with previous therapies used to treat wet AMD.

Before ranibizumab, vision loss resulted from fibrotic scars; but now with ranibizumab, vision loss results from atrophic scars.[7] Possible explanations included a subset of patients in whom normal disease progression ensued once the macula was dried or who were exquisitely sensitive to anti-VEGF therapy and progressed to macular atrophy because of the therapy. Interestingly, in all subsequent anti-VEGF trials using monthly dosing, as in the ANCHOR and MARINA trials, about 10 percent of patients lost at least three lines of vision after two years.



Geographic Atrophy and the CATT Trial

In the CATT trial, which compared intravitreal bevacizumab (Avastin, Genentech) with ranibizumab, both anti-VEGF drugs were beneficial, but eyes that had monthly injections exhibited more geographic atrophy (GA) than as-needed (PRN) injections regardless of the drugs. Moreover, ranibizumab was associated with a significantly higher risk of forming GA than bevacizumab regardless of treatment regimen.[4]

Juan E. Grunwald, MD, and colleagues evaluated risk factors for development of GA using color fundus, FA and OCT images from trial patients. They found that a higher rate of residual fluid on OCT corresponded to a lower the rate of GA, which suggested that excessive drying of the macula might promote development of GA.[8] Additional

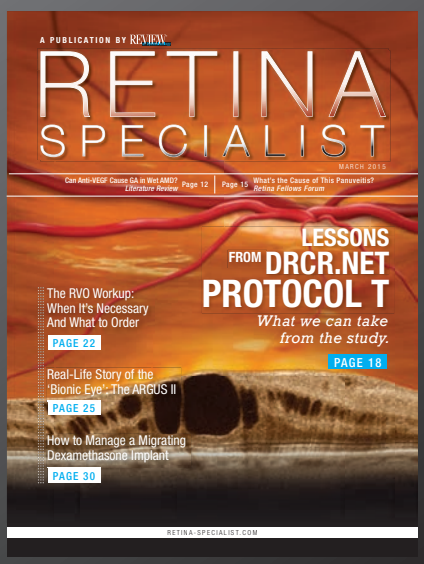
Figure. Development of geographic atrophy in eyes with neovascular age-related macular degeneration after two years of anti-vascular endothelial growth factor therapy. A1, Choroidal neovascularization at baseline on color fundus photography. A2, Classic CNV (white arrow) at baseline on fluorescein angiography. A3, Optical coherence tomography showing at baseline the CNV lesion with prominent intraretinal fluid (white arrow). A4, At two years of follow-up, CFP depicts a large GA lesion in the area of the previously active CNV (black arrow) and an additional small area of GA superior to the baseline CNV (white arrow). A5, At two years of follow-up, FA shows areas of hyperfluorescence with well demarcated margins corresponding with the areas of GA in A4. A6, An OCT scan showing at two-year follow-up increased choroidal signal penetration. ***(Used with permission of Elsevier)***

NEW REVIEW PUBLICATION!

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.



The new addition to the *Review* family serves the entire Retina Specialist marketplace.

Look for your issue in the mail:

» **MARCH**

» **JUNE**

» **SEPTEMBER**

» **NOVEMBER**

For inquiries contact

RETINASPECIALIST@JOBSON.COM

Advertising opportunities

JAMES HENNE • PUBLISHER

Email: jhenne@jobson.com • Phone: (610) 492-1017

evidence from CATT also supported the effect of dosing frequency on GA formation.

When subjects were switched from monthly to PRN injections after year one, the switched group had lower rates of GA under PRN therapy. Moreover, this lower rate was similar to the second-year rate of GA in those who received PRN therapy for two years but lower than the second-year rate of GA in subjects who continued with monthly therapy in the second year.[8]

Notably, visual acuities in year two were similar in the ranibizumab and bevacizumab groups, presumably because most of the GA that developed did not involve the central macula. Multivariate analysis identified baseline risk factors associated with GA development to be visual acuity <20/200, retinal angiomatous proliferation (RAP) lesions, GA in the fellow eye and intraretinal fluid.[8]

A Closer Look at GA

A later analysis by Dr. Grunwald and co-authors used color and FA images to evaluate the growth rate and location of GA in subjects, whether or not they had GA at baseline.[9] Like the previous cohort study, this analysis found the GA growth rate was significantly greater with ranibizumab than bevacizumab with no significant genetic associations.[8,9] In this study, the GA growth rate did not differ between dosing regimens.

GA growth rates were higher with each millimeter the GA margin was from the foveal center, or with greater proximity of GA to the MNV, a history of GA in the fellow eye and the presence of predominantly classic lesions rather than minimally classic and occult lesions.[9] A retrospective study of GA in patients who received bevacizumab, ranibizumab and/or aflibercept (Eylea, Regeneron) by Luna Xu, MD, and colleagues, also found that the risk for GA was significantly higher in RAP lesions (type 3 MNV) and lower in occult lesions. They also reported a trend toward GA with greater number of injections, but it was not statistically significant.[10]

Gui-Shuang Ying, PhD, and colleagues performed another retrospective cohort analysis of the CATT data looking at patient factors that led to sustained vision loss at two years. Bevacizumab treatment was among the baseline factors independently associated with a significantly higher incidence of sustained vision loss. However, they found foveal scarring tended to cause vision loss more often in the bevacizumab-treated eyes while foveal GA tended to be the cause more often in the ranibizumab-treated eyes. However, these findings were not statistically significant. This study did not find any statistical difference between the monthly and PRN dosing groups.[11]

IVAN was another large prospective clinical trial comparing continuous and discontinuous regimens with bevacizumab and ranibizumab. Unlike the CATT cohort analysis, the percentage of participants with incident GA in IVAN did not differ significantly between drug groups. However, the IVAN analysis did show significantly higher rates of GA with continuous treatment compared with discontinuous treatment, which was similar to the CATT findings.[5]

A small retrospective study by Erika Tanaka, MD, and colleagues followed eyes with AMD and MNV for 3.5 years, longer than CATT or IVAN. They reported that GA did not develop outside the original boundaries of MNV during anti-VEGF treatment unless the eye had GA outside these boundaries at baseline. They also showed that eyes demonstrating enlargement of GA outside the original MNV boundaries appeared to manifest enlargement of preexisting GA, just as fellow eyes did when they observed the natural evolution of GA in the absence of MNV.[12]

Similarly, in a retrospective case series analyzing FA and OCT images, Roomasa Channa, MD, and colleagues reported that a majority of eyes developing GA after anti-VEGF therapy did so in areas occupied by MNV while in other eyes GA was present before treatment started. They found that no eyes developed atrophy outside of or adjacent to areas of prior MNV.[13] Whether autofluorescence would be better imaging for studying GA progression in eyes undergoing anti-VEGF, as Nishant Kumar, MBBS, and colleagues suggested, remains to be seen.[14]

Why Does GA Form?

Despite existing prospective and retrospective studies, it remains

(Continued on page 36)

Bascom Palmer Eye Institute
UNIVERSITY OF MIAMI HEALTH SYSTEM

Dr. Rosenfeld is professor at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. He has been the principal investigator and study chair for several clinical trials involving wet and dry AMD. Dr. Ramenaden is a medical retina fellow at Bascom Palmer.

What's the Cause of This Panuveitis?

Sensitivity to light, pain and blurry vision persisted for two weeks.

By Andrew W. Browne, MD, PhD, Jiun Do, MD, PhD, and Damien C. Rodger, MD, PhD

A 37-year-old Hispanic woman came to the Los Angeles County Hospital/University of Southern California emergency department complaining of a painful, burning sensation and redness in her right eye with blurry vision. The symptoms began two weeks earlier and worsened until she developed a pressure-like headache.

She complained of sensitivity to light and was experiencing night sweats, fevers and cough. She denied recent weight loss, changes in bowel habits, chest pain, difficulty breathing, rashes or changes in sensorium. She said that she had normal vision in both eyes since childhood until three years earlier, when she had a similar episode of painful vision loss in her left eye. She vaguely recalled using an eye drop at the time and had eventual resolution of the irritation and pain, but resultant poor vision in that eye.

History

In addition to the right eye pain, the patient reported pain along her entire left leg and lower back for about one year. She reported a history of hypothyroidism, dyslipidemia and depression, and also noted particularly heavy menstrual periods. She had no systemic or current ophthalmic medication use. Her family history was negative. She denied tobacco, alcohol or illicit drug use. She was allergic to ibuprofen.

Examination

The patient was slightly overweight and in no apparent distress. BCVA was 20/200+1 OD and 20/200+1 OS. Intraocular pressure was within normal limits OU. Pupils were 4 mm OD and 2.5 mm OS, and the amount of anisocoria was equal in both light and dark. She had a sluggishly reactive pupil and a relative afferent pupillary defect (APD) OD, and a normally round and reactive pupil OS. Brightness sense OD was 40 percent of OS, and she reported red desaturation OD. She could not see the Ishihara color plate OD, but she correctly identified six of eight plates OS. She had no pain with eye movement.

The slit lamp examination OD was significant for diffuse conjunctival injection accompanied by diffuse, fine keratic precipitates and 3+ anterior chamber cell. The iris had developed a fibrinous strand along the pupillary margin, but the lens was clear. The anterior segment OS was unremarkable without evidence of prior inflammation.

A dilated exam OD revealed a hazy view secondary to heavy vitreous cell, sometimes in clumps, but the optic nerve appeared pink, sharp and well-perfused. The macula appeared grossly flat, the vessels appeared perfused, but we could not adequately visualize the periphery. The left eye had no vitreous cell, a normally demarcated optic nerve head with a fibrous tuft extending into the vitreous and a full-thickness macular hole that appeared chronic. The vessels OS were mildly attenuated, and far in the periphery contiguous bands of retinal fibrosis were visible (*Figure 1*).

Diagnosis, Workup, Treatment

This panuveitis involved a broad differential diagnosis and collection of autoimmune and infectious serologies (*Box, page 17*). B-scan ultrasonography of the right eye demonstrated vitreous opacities and a flat retinal profile in all quadrants. Fluorescein angiogram, while of poor quality in the right eye due to media opacity, showed peripheral staining without progressive leakage from the inferotemporal venous arcade, diminished far temporal and nasal capillary perfusion and progressive staining of fibrotic ridgeline tempo-

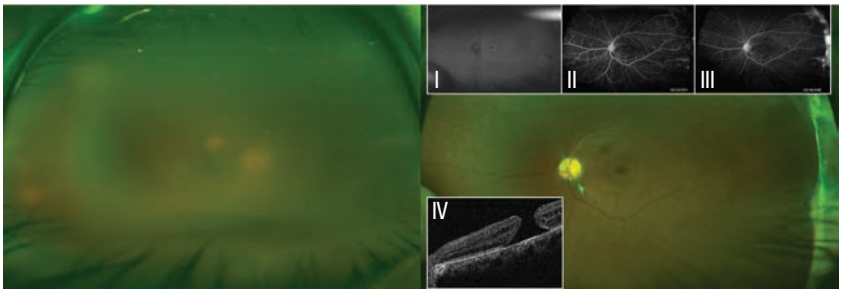


Figure 1. Bilateral widefield fundus photo demonstrated significant vitreous cell OD (left) and a sharply demarcated optic nerve with vitreal fibrous tuft, full thickness macular hole, attenuated vessels and peripheral retinal fibrosis OS (right). Fundus autofluorescence OS showed a hyperfluorescent ring (inset I) while fluorescein angiogram showed peripheral staining without leakage along the inferotemporal venous arcades, reduced temporal and nasal capillary perfusion, and progressive staining of fibrotic ridgeline temporally (II, III). OCT demonstrated the full thickness macular hole (IV).

rally in the left eye. Optical coherence tomography (OCT) could not capture images in the affected eye due to the media opacity, but confirmed a stage 4 full-thickness macular hole with an epiretinal membrane in the left eye (*Figure 2*).

We started her on topical prednisolone q1h and atropine BID to prevent synechia and treat photophobia. She agreed to return the following morning, but instead returned two days later.

At the second visit, her vision remained stable, but the anterior cell had decreased to 1+ with persistent, diffuse fine keratic precipitates. The dilated exam was clear enough to reveal small peripheral white patches in the inferior and temporal peripheries, suggestive of toxoplasmosis or sarcoidosis as a possible granulomatous etiology for her panuveitis. The previously collected complete blood count with differential was normal except for a mild microcytic anemia (later worked up and thought to be due to menorrhagia). Tuberculin PPD, serum RPR and treponemal antibodies were negative, and a chest X-ray normal.

After we discussed the possible viral etiology and the risks of treatment with steroid therapy only, we prescribed acyclovir 800 mg PO five times daily, started oral prednisone (1 mg/kg) daily after 24 hours, and followed closely while awaiting the remaining lab results. On follow-up three days later, the ANA (1:80 speckled) and HSV-2 IgG were significantly elevated while all other serologies, including Lyme, VZV IgM, HSV IgM and HSV-1 IgG, were normal.

We ordered VZV serologies, but the results were delayed. Our suspicion of a herpetic etiology based on the lab results was growing. The improved fundus view demonstrated more obvious retinal whitening and a history of a likely similar but resolved event in the fellow eye that resulted in the permanently decreased vision. We admitted her for intravenous acyclovir and continued oral prednisone 40 mg daily. We also administered an intravitreal injection of foscarnet.

Polymerase chain reaction (PCR) of an anterior chamber paracentesis performed on the day of admission was positive for herpes simplex virus-2 (HSV-2). We diagnosed panuveitis secondary to HSV-2 in the right eye and a compatible history in the left eye resulting in the chronic macular hole secondary to vitreous degeneration.

The patient was kept in the hospital for one week of IV acyclovir and received an additional foscarnet injection on day 12. Follow-up included regular 50° and widefield fundus photography as well as OCT imaging (*Figure 2*) for monitoring. She continues follow-up so we can monitor her for development of retinal necrosis and retinal detachment.

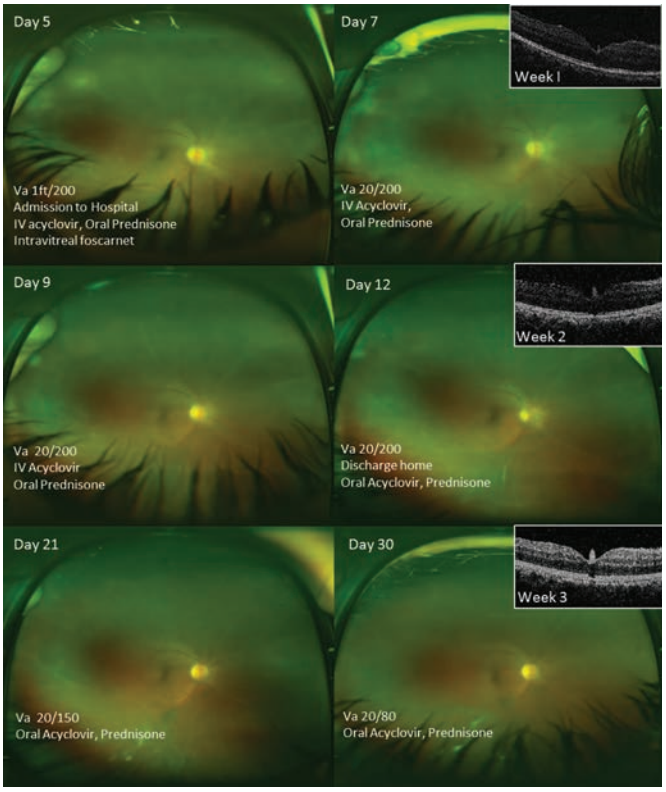


Figure 2. Widefield fundus photography OD demonstrated improvement in vitreous cells on day of admission and visible white lesions peripherally (day 5). Further resolution of vitreous opacity allowed for more detailed examination and identification of arteriolar sheathing. VA continued to improve in correlation with vitreous clearing.

Discussion

Panuveitis has many potential etiologies. In the absence of medical risk factors for immune system compromise, one must maintain a broad differential throughout the workup. Viral panuveitis and associated retinitis can be devastating, especially when left untreated. This presentation is unique given the patient's history of a similar episode in the fellow eye that resolved without interventions but resulted in a macular hole and peripheral retinal fibrosis.

Because our patient presented about two weeks after the onset of symptoms, she had developed an impressive granulomatous panuveitis. Here, we prefer to describe this as a viral panuveitis rather than acute retinal necrosis (ARN).

However, these entities likely exist on a spectrum.

The standard diagnostic criteria for ARN include multiple foci of peripheral retinal necrosis, rapid progression without therapy, circumferential spread, occlusive arterial vasculopathy with prominent inflammation and, possibly, optic neuropathy and painful scleritis.[1]

Our patient demonstrated several discrete foci of retinal whitening with likely prior circumferential spread that we could not fully appreciate because of significant inflammation in the anterior chamber and vitreous. Once the vitritis cleared, arteriolar sheathing was obvious.

This patient also demonstrated other findings characteristic of ARN: an APD, reduced brightness sense and red desaturation. Although she had symptoms for two weeks before her visit, she had no rapid progression of any retinochoroidopathy, possibly thanks to the initiation of therapy.

PCR evaluation of intraocular fluids for HSV, VZV and CMV enhanced our ability to diagnose viral panuveitis and, indeed, ARN, although the lack of inflammation may also have helped differentiate the latter. Historically, ARN has been associated with VZV infections. However, HSV-2 occurs with a higher incidence in younger patients like ours, while VZV is more prominent in older patients.[2]

Uveitic processes require targeted treatment. In infectious etiologies, premature systemic immunosuppressive therapy can accelerate the infection, especially in tuberculosis, syphilis or viral entities. A safe approach involves starting topical corticosteroids for anterior chamber inflammation while initiating laboratory tests with close follow-up.

When clinical suspicion is high and a viral etiology has been confirmed, expeditious, targeted treatment consisting of systemic and, usually, intravitreal antivirals should occur. Systemic steroids may follow soon afterward. The treatment strategy of HSV-2 panuveitis has been adopted from ARN.

Anti-herpetic drugs include older agents like acyclovir and newer drugs like valacyclovir. Oral acyclovir has lower systemic bioavailability than valacyclovir, so dosing of acyclovir for ARN is frequently five-10 days IV before transitioning to oral therapy five times daily for up to three months, a practice established well before high-bioavailability oral agents like valacyclovir were available.[3] Combined intravitreal and systemic antiviral therapy has been associated with better visual outcomes than systemic therapy alone.[4,5] Even after a patient starts antiviral therapy, continued close follow-up is important because multidrug resistance has been known to exist among herpes viruses.[6]

Differential Diagnosis Of Panuveitis

Infectious
- Viral
  - HSV-1, HSV-2, CMV, VZV
- Bacterial
  - *M. tuberculosis, B. hensleae, T. palladium*
- Parasitic
  - Toxoplasmosis

Autoimmune/Inflammatory
- Systemic lupus erythematosus
- Granulomatous polyangitis
- Vogt-Koyanagi-Harada

Conclusion

Effective management of panuveitis requires prompt and accurate identification of the etiology, because the wrong treatment can allow the disease to progress. The differential diagnosis must be broad and include infectious and autoimmune etiologies, especially in immunocompetent patients. Intraocular fluid analysis greatly facilitates diagnosis but may require some time to yield definitive results. In the early phases of evaluation, the clinical context and examination, with particular attention to immune status and risk factors, should guide management. RS

References

1. Holland GN. Standard diagnostic criteria for the acute retinal necrosis syndrome. Executive Committee of the American Uveitis Society. Am J Ophthalmol. 1994;117: 663–667.
2. Van Gelder RN, Willig JL, Holland JN, Kaplan HJ. Herpes simplex virus type 2 as a cause of acute retinal necrosis syndrome in young patients. Ophthalmology. 2001;108:869–876.
3. Taylor SR Hamilton R, Cooper CY, et al. Valacyclovir in the treatment of acute retinal necrosis. BMC Ophthalmol. 2012;12:48.
4. Flaxel CJ, Yeh S, Lauer AJ. Combination systemic and intravitreal antiviral therapy in the management of acute retinal necrosis syndrome (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc. 2013;111:133-144.
5. Yeh S, Suhler EP, Smith JR, et al. Combination systemic and intravitreal antiviral therapy in the management of acute retinal necrosis syndrome. Ophthalm Surg Lasers Imaging Retina. 2014;45:399-407.
6. Dokey AT, Haug SJ, McDonald HR, et al. Acute retinal necrosis secondary to multidrug-resistant herpes simplex virus 2 in an immunocompetent adolescent. Retin Cases Brief Rep, 2014;8:260-264.

USC Eye Institute

Dr. Olmos is an assistant professor of ophthalmology at University of Southern California Eye Institute and the director of the vitreoretinal fellowship at the Keck School of Medicine of USC in Los Angeles.

Drs. Browne and Do are ophthalmology residents at USC Eye Institute/Los Angeles County + USC program. Dr. Rodger is a Heed and Ronald G. Michels Fellow in Vitreoretinal Surgery at the USC Eye Institute.

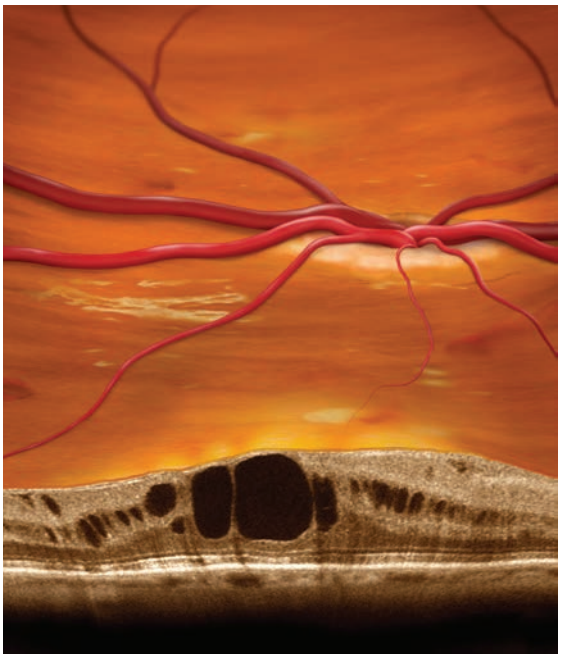


Illustration by Mark Erikson, jirehdesign.com

LESSONS FROM DRCR.NET PROTOCOL T

By Nathan C. Steinle, MD, and Dante Pieramici, MD

What we can take from the study and apply in our clinics.

The National Institutes of Heath-sponsored Diabetic Retinopathy Clinical Research Network (DRCR.net) should be commended for conducting and recently publishing the much-anticipated results of a landmark study comparing three intravitreal anti-VEGF agents in the treatment of diabetic macular edema (DME).[1] Known as DRCR.net Protocol T, these trial results will have a major impact on how we manage our patients with DME.

Protocol T is the first trial to compare the efficacy and safety of the commercially available anti-VEGF drugs used in the treatment of DME: ranibizumab (Lucentis, Genentech), bevacizumab (Avastin, Genentech) and aflibercept (Eylea, Regeneron). Ranibizumab and aflibercept have been approved for DME by the Food and Drug Administration (FDA), whereas bevacizumab is widely used off-label for DME. (In fact, bevacizumab is not FDA-approved for any ocular condition.)

DRCR.net Protocol 1 confirmed the significant cost differences between these agents—Medicare allowable charges range from $1,961 for 2 mg aflibercept to $1,189 for 0.3 mg ranibizumab to $67 for 1.25 mg bevacizumab—but did not answer to any differences in efficacy or safety.

Impetus for Protocol T

Determining a difference between the agents was the impetus for the DRCR.net Protocol T comparative trial. In the retina community, Protocol T has been dubbed the "CATT study for DME." However, Protocol T compared three drugs for DME whereas CATT—the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)—focused on two drugs and dosing strategies (modified PRN versus monthly therapy).[2] Here, we review the findings of DRCR.net Protocol T and explore how they can be applied in the clinic.

Eighty-nine clinical sites in the United States participated in Protocol T, enrolling 660 adults with either type 1 or type 2 diabetes and DME involving the central macula on optical coherence tomography (OCT). Participants were 18 years or older, with vision of 20/32 to 20/320.

Patients did not have to be naive to treatment, but they could not have received anti-VEGF therapy within the last year. Masked participants were treated with 0.05 mL of either 2 mg aflibercept, 1.25 mg bevacizumab or 0.3 mg ranibi-

ABOUT THE AUTHORS

Drs. Steinle (top) and Pieramici are with California Retina Consultants and Research Foundation, Santa Barbara. Dr. Pieramici is a member of the DRCR.net Protocol T writing committee.

zumab, with a primary endpoint of change in visual acuity at one year, with follow-up planned through two years. One eye of each subject was assigned randomly with equal probability to one of the treatment groups.[3]

The treatment regimen was a modified PRN protocol based on vision and OCT findings. During the first six months, participants received monthly injections unless visual acuity was 20/20 or better and OCT central thickness was better than the eligibility threshold. Starting at week 24, irrespective of vision or OCT thickness, an injection was withheld if the patient showed no improvement or worsening after two consecutive injections, but treatment was restarted if vision or OCT thickness worsened. The threshold for improvement/worsening was >4 letter score (one Snellen line) change in visual acuity or a >9 percent change in central OCT thickness. Focal/grid laser was started at or after 24 weeks if DME persisted based on protocol-specific criteria.

Vision Outcomes

The topline DRCR.net Protocol T results revealed improvement in vision from baseline to one year with all three drugs *(Tables 1 and 2, pages 20 and 21)*. Improvement was greatest with aflibercept (+13 letters) than ranibizumab (+11 letters) or bevacizumab (+10 letters), a statistically significant mean difference of 2-3 letters at one year.

This difference appeared to be driven by baseline vision. Half of the study participants had VA of approximately 20/40 or 20/32. In these patients, the mean letter score improvement was +8.3 with ranibizumab, +8.0 with aflibercept and +7.5 with bevacizumab (each pairwise comparison p>0.5).

The Population Burden of Diabetes And Genesis of anti-VEGF Therapy

Diabetes continues to be a growing concern for the American health-care system as its prevalence continues to rise. From 1980 through 2011, the crude prevalence of diagnosed diabetes increased 176 percent in the United States (from 2.5 to 6.9 percent of the population).[11] Some statistical models predict that one-third of Americans will have diabetes by 2050.[12]

Because diabetes is often a disease of working-age adults, it is a tremendous burden on not only the health-care system but also the labor force. In 2011, 63 percent of the adult cases diagnosed within the past year were in individuals ages 40–64 years; and 16% were diagnosed in those ages 18–39 years.[13] Approximately half of these diabetic patients will develop retinopathy, with diabetic macular edema being the number one reason for vision loss.[14]

Thirty years have passed since the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) Report Number 1 was published in 1985, which provided longstanding guidelines for laser photocoagulation use in patients with clinically significant DME.[10] Corticosteroids have also been investigated in the treatment of DME, as triamcinolone,[15] fluocinolone[16] and dexamethasone[17] have all been used as intravitreal therapies for DME.

Recent years have ushered in the era of anti-VEGF drugs for treatment of DME. Well-designed, multicenter clinical trials have shown the benefits of these drugs in the treatment of DME: the RISE/RIDE studies[6] of ranibizumab; the BOLT study[18] of bevacizumab; and the VISTA/VIVID Studies[19] of aflibercept.

The DRCR.net Protocol I study demonstrated the efficacy and superiority of ranibizumab with immediate or deferred laser versus laser alone in the treatment of center-involved DME. Protocol I also revealed that similar visual and anatomic outcomes could be achieved with a PRN (as needed) protocol that reduced the burden of treatment compared to monthly therapy.[20,21] It became very apparent to investigators and clinicians that anti-VEGF therapy was superior to the then "standard of care" for DME—laser photocoagulation.

However, when initial visual acuity was 20/50 or worse, the mean letter improvement was +18.9 with aflibercept, +14.2 with ranibizumab and +11.8 with bevacizumab (p values: aflibercept-bevacizumab <0.001, aflibercept-ranibizumab = 0.003, ranibizumab-bevacizumab = 0.21). OCT central thickness and vision outcomes showed a similar effect favoring aflibercept when baseline retinal thickness was >400 µm.

More injections or other treatments did not drive this relative benefit of aflibercept. In fact, the aflibercept group had one fewer median number of injections[9] than the ranibizumab or bevacizumab groups (p=0.045).[10] Laser was also performed less often with aflibercept (37 percent) than ranibizumab (46 percent) or bevacizumab (56 percent) (p<0.001).

Anatomic Outcomes

The anatomic results paralleled the vision results, with the greatest benefit on reduction in retinal edema seen in the patients treated with aflibercept. At one year, central OCT thickness decreased on average by 169 µm (aflibercept), 147 µm (ranibizumab) and 101 µm (bevacizumab).

Overall, aflibercept reduced retinal edema better than the other two agents (p<0.001) and ranibizumab outperformed bevacizumab (p<0.001). This held true regardless of the presenting vision.

A few key points are worth emphasizing based on the trial results:

- ***First,*** all three agents, on average, improved vision and reduced retinal thickness in patients with center-involved DME. The benefits of treatment could be seen as early as four weeks in some patients, but not

all patients derived a benefit.

• ***Second,*** when patients presented with relatively good vision (20/40 or better), all three drugs resulted in similar vision outcomes at one year, although the anatomic results were better with aflibercept and ranibizumab. Studies have reported that 75 percent of patients with DME present with visual acuity of 20/40 or better.[4,5] Since VAs reported in the study were standardized vision measurements, it is not exactly clear how this translates into the vision measured in our clinics. Standardized refracted visions can be several lines of vision better than typical Snellen visions.

In Protocol T, however, when the vision was 20/50 or less, the benefit for vision favored aflibercept over the other anti-VEGF agents on average. Some may argue that the clinical relevance of a few letters is not very meaningful. Indeed, to one individual such a difference may not be that meaningful. However, the differences between the drugs in this study are in the group averages, and they were statistically significant to a very high level in many comparisons.

Viewed in another way, the chance of three lines of vision improvement in patients with VA of 20/50 or less at baseline was 63 percent greater with aflibercept compared to bevacizumab, and 34 percent greater with aflibercept compared to ranibizumab. Finally, it is important to realize that these represent one-year results to date (and DME is a chronic condition). A planned secondary outcome measure in Protocol T will include change in visual acuity at two years.[3] The second-year data will provide insight into the efficacy and safety of extended therapy and perhaps a better understanding of the relative long-term treatment burden of these agents.

TABLE 1: DRCR.net Protocol T Outcomes for VA >20/50 At Baseline (Letter Score <69)

Visual Acuity Outcomes	*Aflibercept*	*Bevacizumab*	*Ranibizumab*
No. of eyes	102	102	101
VA at baseline			
Mean letter score	56.2±11.1	56.6±10.6	56.5±9.9
Approximate Snellen equivalent	20/80	20/80	20/80
VA at 1 yr			
Mean letter score	75.2±10.9	68.5±13.6	70.7±12.0
Approximate Snellen equivalent	20/32	20/40	20/40
Change from baseline in letter score			
Mean improvement (p=<.0.001)	18.9±11.5	11.8±12.0	14.2±10.6
Central Subfield Thickness (measured with OCT)			
No. of eyes	101	100	99
CST at baseline—µm	452±145	467±155	431±138
CST at 1 yr—µm	238±81	328±154	252±92
Mean change in CST from baseline—µm (p=<.0.001)	–210±151	–135±152	–176±151
CST <250 µm at 1 yr —no. (%)	71 (70)	39 (39)	55 (56)

Adopted from: Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015; Feb 18. [Epub ahead of print].

Questions About Dosing

Some may wonder whether the 0.5 mg dose of ranibizumab might have performed better than the 0.3 mg dose that was used in Protocol T. We will never know for sure, but data from the RISE and RIDE studies[6] found no significant difference between the 0.3 and 0.5 mg doses in terms of efficacy. On the other hand, some smaller studies have demonstrated additional benefit on vision and anatomy in some DME patients when switched to higher dosages of ranibizumab.[7]

A second dosing issue concerns the preparation of bevacizumab. The bevacizumab used in Protocol T was repackaged at a central pharmacy into single-use vials. These vials underwent independent testing for sterility, purity and potency prior to use.[1] Although somewhat unlikely to fully account for differences seen with bevacizumab in this study, significant variability of bevacizumab obtained from compounding pharmacies has been reported and needs to be considered in our "real world patients".[8]

The Safety Issue

With regards to safety, no differences in intraocular inflammation were noted among the three groups, and endophthalmitis was rare (occurring in 0.02 percent of injections). Rates of serious adverse events, deaths, hospitalizations and major cardiovascular events were similar in the three treatment groups. However, a post hoc analysis did find a small but statistically significant increase in reported cardiac and/or vascular adverse events in the ranibizumab group, although it is possible that this finding was a chance event.

The relatively small number of patients in each treatment group (aflibercept, 224; bevacizumab, 218; and ranibizumab, 218) is unlikely to manifest differences in rare serious

adverse events. These three agents have known differences in vivo in regards to their systemic pharmacokinetic profiles,[9] so the continued monitoring of patients for systemic adverse events is prudent, especially in more at-risk DME patients, many of whom, such as those on dialysis, were ineligible for this and other Phase III clinical trials for DME.

The results of clinical trials should serve as guidelines for clinical care. The study results reflect population average outcomes; much individual variability underlies these findings. When considering the individual patient, these data can be instructive, but many additional issues, including cost, factor in the decision of which agent or method of treatment to utilize initially. In addition, this study did not address the benefits of a treatment strategy that begins with one anti-VEGF agent and then switches to another if the result is less than desirable.

The DRCR.net should be commended for the tedious work involved in seeing Protocol T through to completion. It will remain an important study for many years. As retina specialists, it is an exciting time for our ever-growing diabetic patient population. As opposed to the ETDRS era of reducing the rate of vision loss in DME,[10] it is thrilling to offer our patients three agents that offer the chance for significant vision gains. The debate as to how to best use these three agents in DME from the standpoints of treatment burden, cost, efficacy and safety will certainly provide hours of discussion at the upcoming meetings this year.

Disclosures: *Dr. Pieramici disclosed he has been a consultant and adviser to Genentech and has received research funding from Genentech and Regeneron. Dr. Steinle is a speaker for Regeneron and ThromboGenics and receives research funding from Genentech.*

TABLE 2: DRCR.net Protocol T Outcomes VA 20/32–20/40 At Baseline (Letter Score <78–69)

Visual Acuity Outcomes	*Aflibercept*	*Bevacizumab*	*Ranibizumab*
No. of eyes	106	104	105
VA at baseline			
Mean letter score	73.5±2.6	72.8±2.9	73.4±2.7
Approximate Snellen equivalent	20/32	20/40	20/40
VA at 1 yr			
Mean letter score	81.4±8.3	79.9±10.1	81.6±6.8
Approximate Snellen equivalent	20/25	20/25	20/25
Change from baseline in letter score			
Mean improvement (p=<.0.001)	8.0±7.6	7.5±7.4	8.3±6.8
Central Subfield Thickness (measured with OCT)			
No. of eyes	104	103	102
CST at baseline—µm	373±108	363±88	384±99
CST at 1 yr—µm	242±57	294±82	263±84
Mean change in CST from baseline—µm (p=<.0.001)	–129±110	–67±65	–119±109
CST <250 µm at 1 yr —no. (%)	64 (62)	35 (34)	61 (60)

Adopted from: Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015; Feb 18. [Epub ahead of print].

References

1. The Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015; Feb 18. [Epub ahead of print].
2. Martin DF, Maguire MG, Ying GS, et al, CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364:1897-1908.
3. ClinicalTrials.gov. Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab for DME (Protocol T). Available at: https://clinicaltrials.gov/ct2/show/study/NCT01627249. Accessed February 10, 2015.
4. Early Treatment Diabetic Retinopathy Study Research Group. Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. Arch Ophthalmol. 1995;113:1144-1155.
5. Martin DR, Maguire MG. Treatment choice for diabetic macular edema. N Engl J Med. 2015. Feb 18. [Epub ahead of print]
6. Brown DM, Nguyen QD, Marcus DM. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology. 2013;120:2013-2022.
7. Dhoot DS, Pieramici DJ, Nasir M, et al. Residual edema evaluation with ranibizumab 0.5 mg and 2.0 mg formulations for diabetic macular edema (REEF study). Eye (Lond). 2015; Jan. 30 [Epub ahead of print]
8. Yannuzzi NA, Klufas MA, Quach L, et al. Evaluation of compounded bevacizumab prepared for intravitreal injection. JAMA Ophthalmol. 2015; 133:32-39.
9. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. Br J Ophthalmol. 2014; 98:1636-1641.
10. Early Treatment Diabetic Retinopathy Study Research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol. 1985;103:1796-1806.
11. Centers for Disease Control and Prevention. Crude and Age-Adjusted Rate per 100 of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, United States, 1980–2011. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/figage.htm. Accessed February 26, 2015.
12. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr. 2010;8: 29.
13. Centers for Disease Control and Prevention. Distribution of Age at Diagnosis of Diabetes Among Adult Incident Cases Aged 18–79 Years, United States, 2011. Available at: http://www.cdc.gov/diabetes/statistics/age/fig1.htm. Accessed February 15, 2015.
14. Varma R Bressler N, Doan QV, et al. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA Ophthalmol. 2014;132: 1334-1340.
15. Beck RW, Ewards AR, Aiello LP, et al. Diabetic Retinopathy Clinical Research Network (DRCR.net) Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol. 2009;127:245-251.
16. Campochiaro PA, Hafiz G, Shah SM, et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. Ophthalmology. 2010; 117: 1393-1399 e3.
17. Boyer DS, Yoon YH Belfort R Jr, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121:1904-1914.
18. Rajendram R, Fraser-Bell S, Kaines A. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. Arch Ophthalmol. 2012; 130:972-979.
19 Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014;121:2247-2254.
20. Elman, MJ, Ayala A, Bressler NM, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117:1064-1077.e35.
21. Elman MJ, Ayala A, Bressler NM, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. Ophthalmology. 2015;122:375-381.

THE RVO WORKUP

When It's Necessary and What to Order

By J. Michael Jumper, MD

Retinal vein occlusion (RVO), the second most common retinal vascular disease after diabetic retinopathy, affects more than 16 million people worldwide.[1] While the pathophysiology of RVO is not completely understood, the concept of venous thrombosis attributed to Rudolph Virchow 150 years ago remains relevant. He proposed that the triad of vessel wall injury, stasis and coagulopathy were important in the creation of a venous clot. This article reviews the risk factors for RVO and the workup and differential diagnosis of the various types of vein occlusion.

Risk Factors

The main risk factors for RVO include age and systemic vascular disorders. A study in Israel found that the rate of RVO increased exponentially with age—from 0.93 per 1,000 in people age 64 years and younger to 5.36 per 1,000 for those 65 and older.[2] That said, RVO can occur at any age. Sohan Singh Hayreh, MD, PhD, DSc, and colleagues study reported that 49 percent of RVO patients were younger than 65 years old. Also, a significant percentage were younger than 45; 15 percent for central RVO (CRVO), 10 percent for hemi-CRVO and 5 percent for BRVO.[3]

Hypertension, hyperlipidemia and diabetes, all atherosclerotic risk factors, are strongly associated with RVO development. Paul R.A. O'Mahoney, MD, and co-authors calculated the population-attributable risk percentage of these factors and found that 46 percent of RVO cases are due to hypertension, 20 percent due to hyperlipidemia and 5 percent due to diabetes.[4] This emphasizes that, while RVO is indeed an occlusion of a retinal venule, the condition is primarily a consequence of atherosclerosis of the adjacent arteriole.

History and Examination

With this in mind, a systemic evaluation of RVO should include a thorough medical history that investigates atherosclerotic risk factors such as hypertension, hyperlipidemia, diabetes, smoking, obesity and family history of coronary artery disease. An assessment for hypercoagulability risk factors should also take into account estrogen exposure, malignancy, pregnancy or a family history of thrombophilia before age 50 years.

Glaucoma and ocular hypertension are risk factors for CRVO. This underscores the importance of inquiring about a family history of glaucoma and evaluating both eyes for glaucoma, keeping in mind that intraocular pressure (IOP) may be lower in an eye with acute CRVO.[5]

ABOUT THE AUTHOR

Dr. Jumper is in private practice with West Coast Retina in San Francisco, CA. He is co-director of the vitreoretinal fellowship program at California Pacific Medical Center.

Blood pressure should be measured not only in the office but also serially to rule out masked hypertension. Many patients with elevated blood pressure measured in the office will manifest "white-coat hypertension," which carries a strong risk of conversion to sustained hypertension over time.[6]

Any patient suspected of RVO should have a complete ophthalmological examination that includes pupillary assessment and gonioscopy. Dr. Hayreh, and co-authors emphasized four functional vision tests as most helpful in differentiating ischemic and nonischemic CRVO: visual acuity; assessment of a relative afferent pupillary defect measured in log units using neutral density filters; visual field testing; and electroretinography. They stated that the combined data from these tests allows one to determine ischemic status with a high specificity and sensitivity much greater than fluorescein angiography or ophthalmoscopy.[7]

In the acute phase, hemorrhage can create blockage of fluorescence, making it difficult to evaluate vascular perfusion. In RVO with severe hemorrhage, one should consider obtaining color fundus images and deferring angiography until the blood clears and more information can be obtained (*Figure 1*). If a patient with RVO has a fluorescein angiogram, late images of the iris of both eyes can help identify rubeosis.

With advances in imaging technology, the benefits of widefield fluorescein angiography have been shown in detecting peripheral ischemia not otherwise visible.[8] Spectral domain or swept-source optical coherence tomography (OCT) is also important in assessing macular edema in RVO and should be done initially and to follow therapy response.

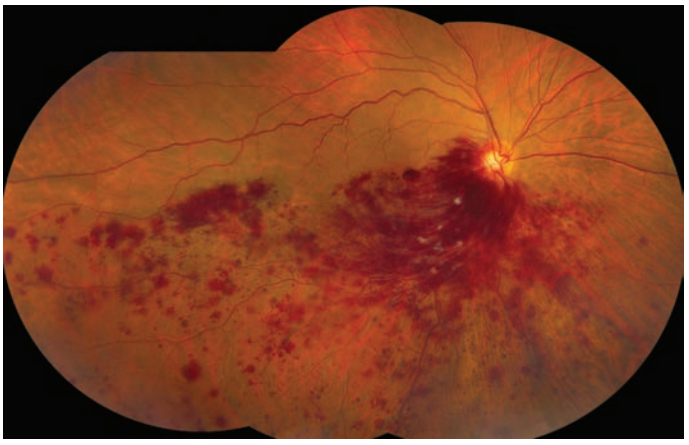


Figure 1. Acute branch retinal vein occlusion in a 61-year-old man shows dense hemorrhage. Fluorescein angiography was deferred because venous blockage would limit its utility.

Table: Coagulation Defects That Cause Arterial and Venous Thrombosis

Abnormality	Arterial	Venous
Factor V Leiden	-	+
Prothrombin G20210A	-	+
Antithrombin deficiency	-	+
Protein C deficiency	-	+
Protein S deficiency	-	+
Hyperhomocysteinemia	+	+
Antiphospholipid antibody syndromes	+	+

Hyperhomoscysteinemia and the antiphospholipid antibody syndromes are the two coagulation defects that cause both arterial and venous thrombosis. This may explain why these defects have been found to be risk factors for retinal vein occlusion.

Controversy of Lab Testing

The most controversial issue in the RVO workup involves the utility of laboratory testing. A reasonable approach is to consider a directed assessment of atherosclerotic risk factors for any patient with an RVO. These include a lipid profile, blood glucose measurement and complete blood count. Atypical features such as intraocular inflammation should lead to further testing for conditions such as sarcoidosis, syphilis and systemic lupus erythematosus.

Over the past two decades, a number of mostly small series and case reports have explored the role of thrombophilic abnormalities in RVO development. Inherited thrombophilic defects include deficiencies of antithrombin, protein C and protein S, factor V Leiden and the prothrombin G20210A mutation.

Acquired risk factors for thrombosis include the antiphospholipid antibody syndrome, myeloproliferative disorders, immobilization, major surgery, malignancy, estrogens and heparin-induced thrombocytopenia. Other risk factors include hyperhomocysteinemia and elevated

factors VIII, IX and XI. Of all of these abnormalities, only hyperhomocysteinemia and the antiphospholipid antibody syndrome are associated with both arterial and venous thrombosis. All other defects are classical venous thrombophilias (*Table, page 23*).

A young patient with a RVO and no identifiable risk factors will typically undergo an extensive battery of tests looking for some or all of the thrombophilia risk factors. Research indicates that this approach is rarely helpful. Danish researcher Prof. Janne Ingerslev said, "Most well characterized risk factors for general venous thrombosis occur sporadically in RVO, and have no major importance in the pathophysiology of RVO."[9]

Italian investigators found no difference between RVO patients and age/sex matched controls in levels of antithrombin, protein C, protein S and homocysteine, lupus anticoagulant, anticardiolipin antibodies or prothrombin polymorphisms.[10] In this same study, arterial hypertension and diabetes were the only factors more common to the RVO patients compared to controls (*Figure 2*).

Dutch investigators found the two risk factors for arterial thrombosis—hyperhomocysteinemia and the antiphospholipid antibody syndromes—were associated with RVO.[11] J. Michael Lahey, MD, and colleagues studied young patients with CRVO and found at least one thrombophilia lab abnormality in 27 percent of subjects, most commonly elevated homocysteine levels and antiphospholipid antibody titers,[12] which supports the Dutch study. In Dr. Lahey's study, the one patient with a systemic disease (protein S deficiency) had bilateral CRVO.

When ordering medical tests, consider how the result will alter treatment. RVO has only two treatment options when the thrombophilia workup is positive. For a patient with hyperhomocysteinemia, one can consider B-complex vitamin supplementation. Randomized studies have failed to prove that reducing homocysteine levels is effective in reducing the risk of stroke, heart attack or other thromboembolic events.[13]

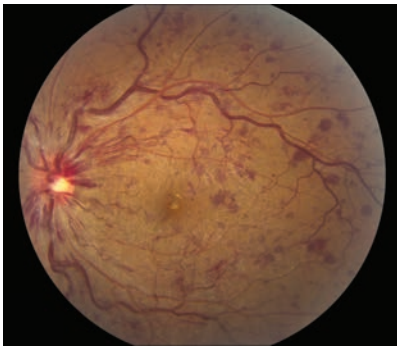


Figure 2. CRVO in a 26-year-old obese man with uncontrolled hypertension and diabetes. This patient did not have a thrombophilia workup.

The only other treatment option for a patient with a thrombophilia is long-term anticoagulation. RVO is unlike a deep venous thrombosis where anticoagulation is used to prevent a downstream pulmonary embolism. Little evidence exists that anticoagulation prevents further ocular vascular occlusion. Anticoagulation has no known benefit on the active clot. Also, in the acute phase of an RVO, anticoagulation may be harmful to the neural retinal tissue by increasing intraretinal hemorrhage, as Dr. Hayreh pointed out.[14]

Conclusion

RVO can happen at any age but is most common in patients over age 65. Vein occlusion shares risk factors of atherosclerosis. The clinician should direct the workup toward evaluation of hypertension, hyperlipidemia and diabetes.

Thrombophilia testing is rarely needed, but can be considered in patients who have a family history of clotting under the age of 50, a personal history of clotting or an unusual presentation such as bilateral simultaneous occlusion.

Consider testing for clotting defects associated with arterial disease, including the antiphospholipid antibody syndrome and hyperhomocysteinemia. Even if a clotting abnormality is discovered, it may or may not be related to the ocular condition. Furthermore, treatment in the acute phase, especially with anticoagulation, may do more harm than good. RS

Disclosure: *Dr. Jumper has no relevant conflicts to disclose.*

References

1. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology. 2010; 117:313.e1–319.e1.
2. David R, Zangwill L, Badarna M, Yassur Y. Epidemiology of retinal vein occlusion and its association with glaucoma and increased intraocular pressure. Ophthalmologica. 1988;197;69–74.
3. Hayreh SS, Zimmerman MB, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. Am. J. Ophthalmol. 1994;117:429–441.
4. O'Mahoney PR, Wong DT, Ray JG. Retinal vein occlusion and traditional risk factors for 4therosclerosis. Arch Ophthalmol. 2008;126:692-699.
5. Hayreh SS, March W, Phelps CD. Ocular hypotony following retinal vein occlusion. Arch. Ophthalmol. 1978;96:827–833.
6. Mancia G, Bombelli M, Facchetti R, et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. Hypertension, 2009;54:226-232.
7. Hayreh SS, Klugman MR, Beri M, Kimura AE, Podhajsky P. Differentiation of ischemic from non-ischemic central retinal vein occlusion during the early acute phase. Graefe's Arch Clin Exp Ophthalmol. 1999;228:201-217.
8. Spaide RF. Peripheral areas of nonperfusion in treated central retinal vein occlusion as imaged by wide-field fluorescein angiography. Retina. 2011;31:829-837.
9. Ingerslev J. Thrombophilia: a feature of importance in retinal vein thrombosis? Acta Ophthalmol Scand. 1999;77:619–621.
10. Di Capua M, Coppola A, Albisinni R, et al. Cardiovascular risk factors and outcome in patients with retinal vein occlusion. J Thromb Thrombolysis. 2010; 30:16-22.
11. Janssen MC, den Heijer M, Cruysberg JR, et al. Retinal vein occlusion: a form of venous thrombosis or a complication of atherosclerosis? A meta-analysis of thrombophilic factors. Thromb Haemost. 2005; 93:1021-1026.
12. Lahey JM, Tunc M, Kearney J, et al. Laboratory evaluation of hypercoagulable states in patients with central retinal vein occlusion who are less than 56 years of age. Ophthalmology. 2002;109:126–131
13. The VITATOPS Trial Study Group. B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. Lancet Neurol. 2010;9:855–865.
14. Hayreh SS. Prevalent misconceptions about acute retinal vascular occlusive disorders. Prog Retinal Eye Res. 2005;24:493–519.

REAL-LIFE STORY OF THE 'BIONIC EYE,' THE ARGUS II

By Ramiro S. Maldonado, MD, Mark S. Humayun, MD, PhD, and Paul Hahn, MD, PhD

The journey of artificial restoration of vision began in 1929 when Otfrid Foerster reported that electrical stimulation of the occipital cortex caused a subject to see a phosphene (a spot of light produced by direct stimulation of the visual system).[1] Years later, in 1956, Graham Tassicker implanted a light sensitive selenium cell behind the retina of a blind patient, transiently restoring the patient's ability to perceive light.[2,3] These first steps laid the foundation for modern artificial retinal implants that are restoring patients' vision today.

Retinal implants can be classified according to their location as epiretinal (tacked to the retinal surface) or subretinal (between photoreceptors and RPE). The Argus II epiretinal prosthesis (Second Sight Medical Products) is currently the only retinal prosthesis approved by the Food and Drug Administration and Health Canada. In Europe, the Argus II, as well as the Alpha IMS (Retinal Implant AG), a light-sensitive subretinal implant, have received the CE mark.

Other retinal implants still in development or clinical trials include the Boston Retinal Implant (Boston Retinal Implant Project), the EpiRet-3 (RWTH Aachen University, Germany) and Intelligent Retinal Implant System (IRIS) (IMI Intelligent Medical Implants GmbH, Germany) (*Table 1, page 26*).

Several alternative implant-based approaches that aim to restore vision are also in early development phases. These include cortical prostheses that directly stimulate the occipital cortex, neurotransmitter-based retinal prostheses and photovoltaic cellular approaches.[4-6] In addition sensory-substitution devices, such as auditory, tactile and tongue-stimulating devices, are also undergoing investigation.[7]

The Argus II Retinal Prosthesis

The Argus II prosthesis is currently the only retinal prosthesis with both FDA and CE approval.[9] This 60-electrode implant is a second-generation device following the Argus I, a 16-electrode implant that was placed in six subjects on an investigative basis at the University of Southern

ABOUT THE AUTHORS

Dr. Maldonado is a resident at Duke University Eye Center, Durham, N.C.

Dr. Humayun is the Cornelius J. Pings Chair in Biomedical Sciences; professor of ophthalmology, biomedical engineering, and cell and neurobiology; director, Institute for Biomedical Therapeutics; and co-director, University of Southern California Eye Institute, Los Angeles.

Dr. Hahn is assistant professor of ophthalmology for vitreoretinal surgery and diseases at Duke University Eye Center.

California starting in 2002 (*Table 2*).

Argus II consists of an external (wearable) and internal (surgically implanted) component. The external equipment consists of glasses, a video processing unit (VPU) and a wired cable (*Figure 1A*). The glasses hold a miniature video camera in the nasal bridge that transmits images to the wired VPU for image processing. The VPU transforms the images to data that are then transmitted wirelessly to the internal implant in the eye.

The implanted component consists of a receiving coil and electronics case secured to the eye in a scleral buckle fashion and the 60-electrode array secured to the retina with a retinal tack (*Figure 1B*).

The data the VPU sends wirelessly to the electronics package stimulates the array to emit small pulses of electricity that excite the remaining viable inner retina cells, including ganglion cells. These artificially stimulated retinal ganglion cells transmit signals through their axons to the lateral geniculate nucleus and then the occipital cortex, which perceives patterns of light. The final step is for patients to piece together these patterns of light into form vision.

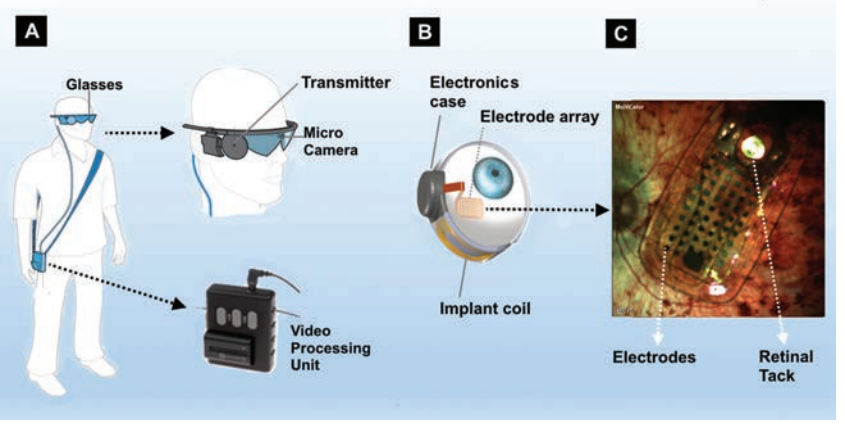


Figure 1. Argus II retinal prosthesis components: Diagram of external components including glasses with micro camera, transmitter (radio frequency coil) and video processing unit (A). Diagram of surgically implanted component including implant coil, electronics case and 60-electrode array (B). Multicolor scanning laser ophthalmoscope view of the array optimally centered on the macula and attached to the retina by a retinal tack (C). ***(A and B courtesy Second Sight Medical Products; C courtesy of Paul Hahn, MD, PhD)***

Clinical Trials

In 2009, the Argus II was FDA-approved as a Humanitarian Use Device intended for treatment of a small patient populations (fewer than 4,000 individuals per year in the United States). To attain this designation, the Argus II was required to demonstrate safety and, on a reasonable basis, probable benefit to health that outweighs the risk of injury or illness.

In the largest prospective, single arm, unmasked, multicenter Argus II study, 30 subjects from 10 medical centers (six in the United State and four in Europe) were implanted with the Argus II on a research basis prior to FDA-approval.[8] Mean age was 58 years (range of 28-77 years). Nine women and 21 men participated. Twenty-nine had a diagnosis of retinitis pigmentosa, and one had a diagnosis of choroideremia. Twenty-nine had bare light perception vision, and one had no light perception. Subjects served as their own control (system on versus off).

Because the profound vision loss in this patient population precluded accurate assessment of visual acuities by conventional methods, such as visual acuity charts, custom end-points were carefully designed in this trial.

Table 1. Characteristics of current retinal implants

	Argus II[8,9]	Alpha IMS[9,10]	Boston Retinal Implant[11]	Epi-Ret-3[12, 13]	Intelligent Medical Implants[9,14]
FDA-approved	Yes	No	No	No	No
CE Mark	Yes	Yes	No	No	No
Method of image capture	External camera	Multiphotodiode array	External camera	External camera	External camera
Array location	Epiretinal	Subretinal	Subretinal	Epiretinal	Epiretinal
Number of electrodes	60	1,500	100	25	49
Array dimension	3 x 5 mm	3.1 x 3 mm	5 x 5 mm	Information not available	Information not available
Electrode size	200 µm	15 x 30 µm	400 µm	100 µm	100-360 µm

Visual acuity was measured by three tests: square localization; direction of motion; and grating visual acuity. The square localization test (*Figure 2A*) assessed the subject's ability to localize a white square on a black screen. The direction of motion test (*Figure 2B*) assessed the subject's ability to determine the direction of motion of a white line moving across a black background. The grating visual acuity test (*Figure 2C*) assessed the ability to identify the orientation of white and black bars of progressively narrowed widths.[8]

In a subsequent study of 21 Argus II subjects, patients were also asked to identify white letters (both individual and of small words) projected over a black background (*Figure 2D*).[15]

Functional vision was evaluated with a "door task" (*Figure 2E*) to assess the patient's ability to find a large piece of black felt hung on a white wall to simulate a doorway and a "line task" (*Figure 2F*) to assess the patient's ability to follow a white line on the floor to simulate the straight lines of a crosswalk or sidewalk.

Additionally, a Functional Low Vision Observer Rated Assessment (FLORA) was performed, in which an independent low vision specialist was asked to observe and create a narrative outlining the patient's use of the device in his/her own home environment.

At up to three years of follow-up, investigators noted improved performance with the system on versus off in square localization, the direction of motion assessment and grating visual acuity. Interestingly, 27 percent of patients regained a measurable visual acuity (grating VA of 2.9 logMAR) with the greatest logMAR of 1.8 (equivalent to 20/1262).[8] Some subjects could also identify letters, even up to a reduced size of 0.9 cm, and a few could correctly identify two, three and four letter words.[15]

The clinical trial also demonstrated functional improvements in both the door and line tasks and subjective improvements in locating doors and windows, sorting laundry, staying within a crosswalk, detecting and avoiding obstacles, locating and tracking people, following lines and edges, and, ultimately, in feeling more socially connected.

In the FLORA assessment, an independent observer noted that 77 percent of subjects had a positive effect from the Argus II, while 23 percent had no positive effect (although no patient had a negative effect). In this trial, safety data showed no permanent impairment, no loss of residual native vision and no mechanical failure of the Argus II device.[8]

Surgery-associated adverse events were noted in nine of 30 patients and included conjunctival erosions, endophthalmitis and hypotony. All events were treated successfully except in one patient with conjunctival erosion resulting in explantation of the Argus II.[8] Many of these complications were attributed to early experiences with the Argus II, and following refinement of the implantation procedure and device itself, an

Table 2. Brief History of the Argus II

- 2002: First Argus I device was implanted at University of Southern California.
- 2007: First Argus II device was implanted in the United States during clinical trials at University of Southern California.
- 2009: Argus II was designated as a Humanitarian Use Device by the FDA.
- 2011: Argus II receives CE mark approval.
- 2011: First commercially available Argus II is implanted at the University Hospital Ophthalmic Department of Pisa, Italy.
- 2013: Argus II receives FDA approval.
- 2014: The first commercially available Argus II in the United States is implanted at the University of Michigan.
- 2015: Argus II receives Health Canada approval.

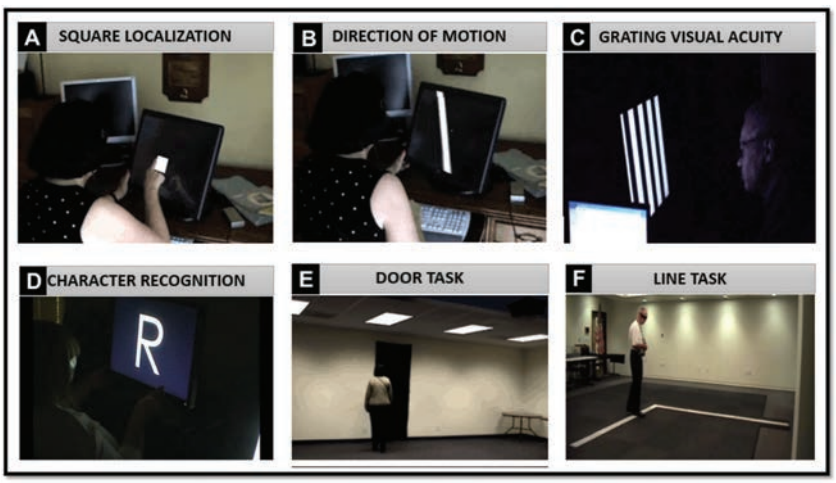


Figure 2. Tests used during Argus II clinical trials to evaluate vision (A-D) and function (E, F). Patient's performance was better with the Argus II retinal prosthesis on versus off in all of these tests. ***(Courtesy of Second Sight Medical Products)***

improved adverse event profile has been reported.[16]

The 'Right Patient'

The Argus II aims to restore rudimentary functional vision to patients with profound vision loss. It is FDA-approved for adults (age 25 years or older) with a diagnosis of retinitis pigmentosa and a history of prior useful vision who have progressed to bare light perception or no light perception vision in both eyes (*Table 3*).

Contraindications include comorbidities that would prevent the implant from functioning properly (e.g., optic nerve disease, cortical blindness, history of retinal detachment, retinal vascular occlusion, trauma or severe strabismus). Other contraindications include conditions that would prevent adequate implantation of the Argus II, such as conjunctival thinning, axial length <20.5 mm or >26 mm (given the fixed intraocular cable length) and conditions that prevent implant visualization such as corneal opacities.

Finally, the implant is not recommended in patients with a tendency to eye rubbing or with a metallic or active implantable device in the head such as cochlear implant.

Surgical Technique and Postoperative Follow-up

The implantation procedure for the Argus II was refined to require a combination of skills, many of which are familiar to the trained vitreoretinal surgeon (*Table 4*). The implant is secured to the wall of the eye in a fashion similar to a scleral buckle. The array is then inserted through a 5.5-mm sclerotomy and secured over the macula in a unique technique involving the use of a retinal tack to secure the implant to the retina-choroid-sclera. Care around the delicate electronics is paramount, and precisely measured external fixation of the implant is critical to allow optimal centering of the array over the macula. A patch graft is used to cover the electronics case, and suture tabs and complete closure of the overlying conjunctiva and tenon's are important.

Table 3. Argus II Current Eligibility Criteria

- Adults, age 25 years or older.
- Bare light or no light perception in both eyes due to retinitis pigmentosa.
- Previous history of useful form vision
- Aphakia or pseudophakia (if present, the natural lens will be removed during the implant procedure).

The Argus II implant is intended to be implanted in a single eye, typically the worse-seeing eye.

Postoperatively, standard follow-up is indicated to monitor for adverse events, particularly hypotony, conjunctival erosion and endophthalmitis. Standard postoperative eye drops are administered without extended steroid or antibiotic therapy beyond the postoperative period.

Within a few weeks following surgical implantation, the patient's video processing unit (VPU) is customized to optimize each electrode according to the patient's residual thresholds of stimulation. The VPU can be programmed with multiple, easily adjustable settings to optimize edge detection or maximize visualization of high contrast items, for example. This fitting process occurs over several days, after which the external glasses are turned on to stimulate the implanted array for the first time.

Following programming, the patient undergoes ongoing low vision rehabilitation and orientation and mobility training in conjunction with a low vision specialist and occupational therapist to learn how to maximize the use of the device.

A Patient's Perspective

Larry, a 66-year-old man, was the seventh patient to receive a commercially available Argus II retinal prosthesis in the United States. He started to lose vision in his early 30s, when he was diagnosed with retinitis pigmentosa by Dr. Robert Machemer at the Duke Eye Center in Durham, N.C. At that time, Larry was informed that no medical treatment would prevent his vision loss, which slowly progressed toward profound blindness over the years.

For the past 10 years or so, Larry could not identify if ambient lights were on or off, although clinical assessment with a specialized photoflash test confirmed residual bare light perception vision. Larry was well adapted to his vision loss, but he hoped for more.

One of his favorite yearly traditions was to experience the fireworks live with his youngest granddaughter sitting on his lap, and he felt that if could "see" the flashes of fireworks for the first time with her, it would all be worthwhile. Larry was well aware of the limitations of the device and the need for rigorous postoperative training, and he was eager for the prospect of any improvement.

Following successful implantation, Larry's journey with the Argus II has been marked with excitement. Three weeks postoperatively, following programming of his VPU, his device was turned on, resulting in visualization of phosphenes (perception of seeing light flashes in response to controlled electrical stimulation of the retina) for the first time in years. (A video of his experience is available on YouTube at https://www.youtube.com/watch?v=CiyGOUHD2nI).

His wife describes what happened one day later: "As we were driving home, Larry turned the device on.

He was able to distinguish where the streetlights were, a lit billboard and headlights as they came our way. It was truly amazing!"

One of the most gratifying early experiences for Larry was with lamps in his house. "Before the Argus II, I could not tell if a lamp in the house was on or off without burning my hands," he said. "Now with the Argus II, I can go around and turn lamps off that are on. That is pretty functional for me!"

Several weeks into his device, he tried joining his granddaughter in playing Velcro darts (*Figure 3*). As his wife describes, "I told him he should put on his glasses and see if he could tell where the dart board was. He put on his glasses. Shocker! He found the dart board and started playing. He rarely missed. That's about as much fun as he has had in a long time playing a game. He wanted to try it again tomorrow and the next day and the next day! To be truthful, I was kind of surprised that he could see it as well as he did. But the darts didn't lie. He did well!"

With ongoing low vision rehabilitation, Larry has increasingly learned how to use his device to maximize his experiences with it. He is able to identify the location of doorways and windows, he can reach out to find and touch his wife's and grand children's faces. He should certainly be able to see the flashes of fireworks. His exploration of a new world with visual stimulation has just begun.

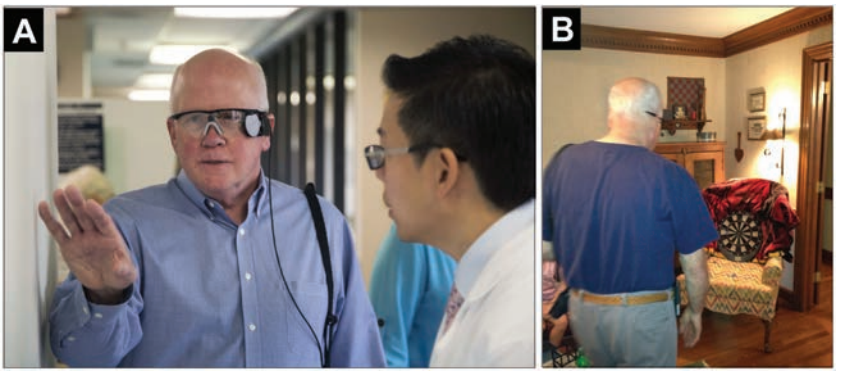


Figure 3. Larry, the seventh U.S. patient to receive a commercially available Argus II retinal prosthesis, is wearing and using the Argus II and describing to Dr. Paul Hahn his visual experiences (A). At his home, Larry plays Velcro darts with the Argus II (B); as his wife explains: "He found the dart board and started playing. He rarely missed. That's about as much fun as he has had in a long time playing a game."

Table 4. Argus II Surgical Technique

The initial surgery to implant the Argus II may take 3-5 hours (4 hours on average). Surgical steps include:

- Crystalline lens removal, if applicable.
- Peritomy and muscle isolation.
- Placement of extra-ocular portion of device.
- Anchoring of suture tabs.
- Securing scleral band.
- Vitrectomy.
- Creation of sclerotomy to insert array.
- Tacking of array over macula.
- Application of patch graft and closure.

A Future for Artificial Vision

The approval of the Argus II marks an exciting era of enthusiasm and hope for physicians and patients in the treatment of vision previously considered permanently lost.

Although it provides far from natural vision and is currently only approved for patients with profound vision loss from retinitis pigmentosa, the Argus II and other retinal implants and their early successes encourage development of future technologies to provide improved safety and durability, image resolution and applications in other diseases. RS

Disclosures: *Dr. Humayun is a consultant, equity owner and holds patents with Second Sight Medical Products, from whom he also receives lecture fees and grant support. Dr. Hahn is a consultant to Second Sight.*

References

1. Foerster O. No Beitrage zur Pathophysiologie der Sehbahn und der SehsphareTitle. J Psychol Neurol. 1929;39:463-485.
2. Tassicker GE, inventor. Retinal stimulator. US patent 2760483. 1956:2,760,483.
3. Brindley GS, Lewin WS. The sensations produced by electrical stimulation of the visual cortex. J Physiol. 1968;196:479-493.
4. Torab K, Davis TS, Warren DJ, House PA, Normann RA, Greger B. Multiple factors may influence the performance of a visual prosthesis based on intracortical microstimulation: nonhuman primate behavioural experimentation. J Neural Eng. 2011;8:35001.
5. Bi A, Cui J, Ma Y-P, et al. Ectopic expression of a microbial-type rhodopsin restores visual responses in mice with photoreceptor degeneration. Neuron. 2006;50:23-33.
6. Peterman MC, Mehenti NZ, Bilbao K V, et al. The Artificial Synapse Chip: a flexible retinal interface based on directed retinal cell growth and neurotransmitter stimulation. Artif Organs. 2003;27:975-985.
7. Chekhchoukh A, Goumidi M, Vuillerme N, Payan Y, Glade N. Electrotactile vision substitution for 3D trajectory following. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2013;2013:6413-6416.
8. Humayun MS, Dorn JD, da Cruz L, et al. Interim results from the international trial of Second Sight's visual prosthesis. Ophthalmology. 2012;119:779-788.
9. Chuang AT, Margo CE, Greenberg PB. Retinal implants: a systematic review. Br J Ophthalmol. 2014;98:852-856.
10. Stingl K, Bartz-Schmidt KU, Besch D, et al. Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS. Proc Biol Sci. 2013;280:20130077.
11. Rizzo JF 3rd. Update on retinal prosthetic research: the Boston Retinal Implant Project. J Neuroophthalmol. 2011;31:160-168.
12. Roessler G, Laube T, Brockmann C, et al. Implantation and explantation of a wireless epiretinal retina implant device: observations during the EPIRET3 prospective clinical trial. Invest Ophthalmol Vis Sci. 2009;50:3003-3008.
13. Menzel-Severing J, Laube T, Brockmann C, et al. Implantation and explantation of an active epiretinal visual prosthesis: 2-year follow-up data from the EPIRET3 prospective clinical trial. Eye (Lond). 2012;26:501-509.
14. Matthaei M, Zeitz O, Keserü M, et al. Progress in the development of vision prostheses. Ophthalmologica. 2011;225:187-192.
15. Da Cruz L, Coley BF, Dorn J, et al. The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. Br J Ophthalmol. 2013;97:632-636.
16. Rizzo S, Belting C, Cinelli L, et al. The Argus II Retinal Prosthesis: 12-month outcomes from a single-study center. Am J Ophthalmol. 2014;157:1282-1290.

How to Manage a MIGRATING DEXAMETHASONE INTRAVITREAL IMPLANT

By Rahul N. Khurana, MD

The dexamethasone intravitreal implant (DEX implant; Ozurdex, Allergan Inc.) has been approved for the treatment of macular edema secondary to retinal vein occlusion, noninfectious uveitis affecting the posterior segment and diabetic macular edema (DME).[1-3] The DEX implant is a non-tethered biodegradable sustained release implant containing 0.7 mg dexamethasone in the Novadur (Allergan) solid polymer drug-delivery system. With the approval for DME in 2014, retina specialists are using the DEX implant more frequently for complicated cases, such as those that do not respond to anti-VEGF therapy and for DME in vitrectomized eyes.[4]

However, these implants can occasionally migrate into the anterior chamber, causing vision-threatening complications that involve permanent corneal decompensation.[5-7] The initial reports were in aphakic eyes, and authors speculated that aphakia is the main risk factor for anterior chamber complications.[6]

Risk Factors for Migration

The largest series of DEX implant anterior chamber migration reviewed the risk factors, clinical outcomes and management strategies.[7] The authors described 15 patients with 18 episodes of anterior chamber migration of the DEX implant. All eyes had been treated for cystoid macular edema from various causes including central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), non-infectious uveitis and DME. All cases had a history of vitrectomy and either an absent or defective lens capsule. All 15 patients had prior pars plana vitrectomy (PPV) and 14 (93 percent) had no lens capsule. Six eyes were aphakic, four had an anterior-chamber intraocular lens (ACIOL) (*Figure*), two had a scleral-fixated IOL, two had a posterior-chamber IOL (PCIOL) and one had an iris-fixated PCIOL. Five patients had prior uncomplicated dexamethasone implant injections with the same lens and capsule status.[7]

The average number of days from injection to migration was 13 (range, five to 44 days). Corneal edema was the most significant vision-threatening complication, which presented in all but two cases. In all the patients presenting with corneal edema, the time from injection to migration was 19 days or less.[7]

In one case without corneal edema, the implant was lodged between the iris and the lens capsule, so it was not in proximity to the corneal endothelium. In the other case with-

ABOUT THE AUTHOR

Dr. Khurana is a partner with Northern California Retina Vitreous Associates and a clinical assistant professor of ophthalmology at the University of California, San Francisco.

out corneal edema, the implant had migrated anteriorly 44 days after injection, presumably after significant degradation.

When the implant migrated into the anterior chamber, one patient was observed, four were positioned supinely, one underwent YAG fragmentation and 11 underwent surgical removal involving either forceps, aspiration of implant fragments or repositioning into the posterior chamber. The implant can be friable and so can be a challenge to remove in one piece. It was aspirated with a vitreous cutter.[7]

The average interval from diagnosis of migration to surgical removal of the implant was 3.5 days, with earlier intervention associated with a lower likelihood of permanent corneal edema. Among the 14 patients with corneal edema, 10 (71 percent) had no resolution of the corneal edema and six (43 percent) required corneal transplantation.[7]

In this report of 15 patients with anterior chamber migration of the DEX implant, the high rate of permanent corneal edema development is most concerning. Anterior migration occurred in eyes that were aphakic and pseudophakic with the lens capsule either absent or compromised. Surgery was successful in removing the implant, but had limited success in reversing the corneal edema. Treating retina specialists should be aware of this potential adverse event, and that the possible risk factors include not just aphakia, but any degree of compromised or absent capsule, even with an IOL and a history of vitrectomy surgery.

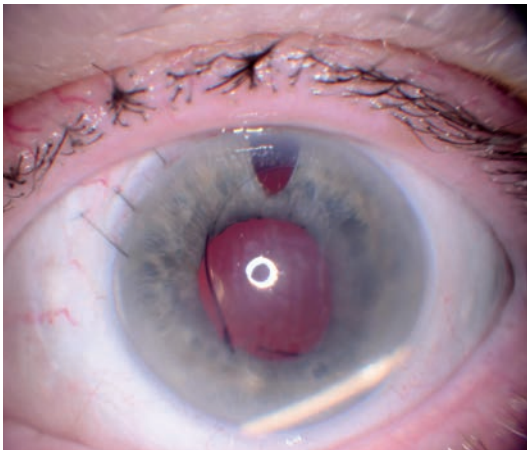


Figure. In this eye with an anterior chamber intraocular lens, the dexamethasone implant has migrated into the anterior chamber and corneal edema is present. ***(Image courtesy of David J. Parks, MD)***

Anterior chamber migration of the DEX implant was first reported in a vitrectomized eye with an ACIOL and then in aphakic vitrectomized eyes.[5,6] Subsequently, cases involving PCIOLs were also published.[8-10] In contrast, the Phase III clinical studies involving the DEX implant for RVO and DME reported no cases of anterior chamber migration of the steroid implant in 2,335 patients.[1,3] However, the exclusion criteria for entry into the study included aphakia or ACIOL.

A smaller study that examined the DEX implant for uveitic cystoid edema in vitrectomized eyes of 17 patients reported one case of anterior chamber migration for an incidence of 6 percent.[11] Approximately 20 cases have been reported in the literature in addition to the large series described here.[5,6,8-19]

Anterior chamber migration occurs in eyes with aphakia and pseudophakia with anterior chamber, iris-fixated, scleral-fixated and intracapsular posterior chamber IOLs. The two common risk factors in the previously referenced series were a defective or absent posterior capsule and a prior vitrectomy.[7] Nevertheless, the presence of both of these risk factors does not necessarily guarantee that implant migration will occur.

Five patients in the previously referenced series had prior uncomplicated DEX implant injections without anterior chamber migration and had the same lens and capsular status when migration occurred later.[7] Further, one study speculated that zonular dehiscence and large peripheral iridotomy may play a role when the implant migrates into the anterior chamber.[19] We should monitor patients with these conditions closely for migration of the implant.

To prevent migration of the DEX implant in patients with these risk factors, some investigators have proposed a technique of scleral fixation of the DEX implant in the vitreous cavity with a 10-0 nonabsorbable polypropylene suture.[20]

Complications of Migration

Corneal edema is the most serious complication of DEX implant migration in the anterior chamber. In the series noted earlier, 16 cases (89 percent) of corneal edema were observed at presentation among the 18 episodes of DEX implant migration.[7] In 10 patients (71 percent), the corneal edema did not spontaneously resolve despite implant removal, and six (43 percent) were referred for keratoplasty.[7]

The mechanism of corneal edema could be endothelial decom-

Clinical Pearls

- Combination of vitrectomy and lens capsular/zonular defect puts patients at risk.
- IOL will not preclude implant migration.
- Migration puts patients at high risk for permanent corneal edema and decompensation.
- Urgent removal of the migrated implant with corneal edema is recommended.

pensation either due to chemical toxicity from any component of the DEX implant (dexamethasone, lactic acid or glycolic acid) or mechanical trauma from a rigid object. Specular microscopy has demonstrated corneal endothelial cell loss when the DEX implant migrates in the anterior chamber.[10]

High doses of dexamethasone are cytotoxic to corneal endothelial cells, inducing both apoptosis and necrosis.[21] Corneal edema occurs with early migration (within less than three weeks).[7]

Two previously reported cases in which the implant migrated at five weeks and three months after injection did not develop corneal edema.[6,12] With late migration (occurring after three weeks), the implant may have degraded enough to cause minimal corneal toxicity from the dexamethasone, but further study is required.

Anterior chamber migration is not unique to the DEX implant. It was first reported after intravitreal injection of triamcinolone acetonide, resulting in a pseudohypopyon with the steroid crystals in the anterior chamber.[22,23] Anterior chamber migration is also possible with another intravitreal device involving the fluocinolone acetonide implant (Iluvien, Alimera Sciences).

The FDA approved Iluvien in 2014 for treatment of DME in patients previously treated with corticosteroids who did not have a rise in intraocular pressure. It contains 0.19 mg of fluocinolone acetonide and is injected into the vitreous cavity. Because it is a free-floating implant (and non-tethered like the DEX implant), Iluvien can migrate into the anterior chamber in vitrectomized eyes. Cases of anterior chamber migration have been reported, but none have been published.

The package insert for Iluvien carries a warning that notes that patients in whom the posterior capsule is either absent or torn are at risk of implant migration into the anterior chamber. The incidence of corneal issues with the fluocinolone acetonide implant that migrates anteriorly is not known.

However, corneal issues have been reported with another fluocinolone acetonide intravitreal implant, Retisert (Bausch + Lomb), which has been reported to migrate anteriorly and cause corneal edema.[24,25] Retisert does have a larger dose of fluocinolone acetonide than Iluvien—0.59 mg vs. 0.19 mg—and both of these large doses of steroid may be toxic to the corneal endothelium.

Retina specialists should be aware of this potential complication with the fluocinolone acetonide implants and exercise caution in the setting of anterior chamber migration and corneal edema.

Reports of Dexamethasone Implant Migration in the Literature

Type of analysis	Episodes reported (n)	History	Lens status
Case report[5]	1	Prior anterior vitrectomy	ACIOL
Retrospective review[6]	3	Post-lensectomy vitrectomy	Aphakia
Retrospective review[7]	18 (15 patients)	Absence of lens capsule and prior pars plana vitrectomy	Aphakia (6); ACIOL (4); scleral-fixated PCIOL (2); PCIOL (2); iris-fixated PCIOL (1)
Case report[8]	1	Prior vitrectomy	Aphakia
Case report[9]	1	Prior pars plana vitrectomy	Scleral-fixated PCIOL
Case report[10]	3	Prior pars plana vitrectomy	2 ACIOL and 1 PCIOL with zonular rupture
Retrospective review[11]	1	Uveitic CME and pars plana vitrectomy	Aphakia
Case report[12]	1	Peripheral iridotomy	PCIOL
Case report[13]	1	Prior pars plana vitrectomy	Iris-claw ACIOL lens implantation
Case report[14]	1	Chronic CME secondary to idiopathic intermediate uveitis	NA
Case report[15]	1	Pseudophakic CME; ruptured lens capsule	ACIOL
Case report[16]	1	Macular edema due to CRVO	Scleral-fixated PCIOL
Case report[17]	1	Hemi-retinal vein occlusion, neovascular glaucoma, hyphema, recurrent vitreous hemorrhage, pars plana vitrectomy, panretinal photocoagulation, Ahmed valve implant	Pseudophakia
Retrospective review[18]	4	Noninfectious posterior uveitis	Aphakia
Case report[19]	1	Noninfectious posterior uveitis	PCIOL with zonular compromise

Management Options

A few management options exist in the setting of anterior chamber migration of the DEX implant. Observation may be considered in the absence of corneal edema. Supine positioning of the patient and pupil dilation in aphakic eyes may allow the implant to fall back posteriorly.[14]

Pilocarpine may reduce pupil size either primarily or following repositioning to minimize the chance of the implant moving anteriorly, but recurrent migration may still occur.[6] A slit-lamp procedure using a needle to reposition the implant posteriorly is an option as well, but the implant may return.[13] Typically, no corneal edema is present with late migration (after three weeks), so in these cases observation could be employed.

If the implant does migrate into the anterior chamber and corneal edema ensues, it should be removed as soon as possible to prevent corneal decompensation. Early removal of the DEX implant has been known to reduce the likelihood of permanent corneal endothelial damage.[7] This suggests that removing the implant earlier is better for the corneal endothelium and preventing chronic corneal edema.

With regards to the surgical technique for removing the DEX implant, an anterior segment approach using viscoelastic to coax the implant toward a limbal incision can be used if the implant is not friable. Once it moves to the incision, the implant can be removed by gently grasping it with a forceps.

An elegant surgical technique involving standard vitreoretinal instrumentation, viscoelastic, a modified Sheets glide and angled forceps to avoid fragmentation of the implant and limit iatrogenic morbidity has also been described.[26] A helpful surgical pearl involves using an angled McPherson forceps to grasp the implant parallel to its long axis and avoid dissolution of the implant into multiple particulate fragments.[26]

A friable implant can be difficult to grasp with forceps or other surgical instruments, and it could disintegrate into numerous fragments with minimal manipulation. In these situations, aspiration with a vitreous cutter or similar instrument may be necessary to remove the implant. Be prepared for these scenarios and anticipate the possible need for vitreoretinal instrumentation when attempting to remove the implant.[7]

The package insert for the dexamethasone implant was modified in September 2012 to reflect that contraindications include aphakia and an ACIOL with rupture of the posterior capsule. However, the combination of compromised zonular or posterior capsular integrity and a history of vitrectomy makes anterior migration of the DEX implant more likely.

It is important to emphasize that the presence of an IOL alone will not prevent migration in the absence of an intact posterior lens capsule. When migration occurs, the patient is at risk for corneal edema and decompensation. If corneal edema does occur, I recommend urgent removal of the DEX implant.

Disclosures: *Dr. Khurana disclosed that he is a consultant and investigator for Allergan; a consultant and speaker for Genentech; and a consultant, speaker and investigator for Regeneron.*

References

1. Haller JA, Bandello F, Belfort R Jr., et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology. 2010;117:1134-1146 e1133.
2. Lowder C, Belfort R Jr., Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Arch Ophthalmol. 2011;129:545-553.
3. Boyer DS, Yoon YH, Belfort R Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121:1904-1914.
4. Boyer DS, Faber D, Gupta S, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina. 2011;31:915-923.
5. Pardo-Lopez D, Frances-Munoz E, Gallego-Pinazo R, Diaz-Llopis M. Anterior chamber migration of dexamethasone intravitreal implant (Ozurdex®). Graefes Arch Clin Exp Ophthalmol. 2011.
6. Bansal R, Bansal P, Kulkarni P, Gupta V, Sharma A, Gupta A. Wandering Ozurdex® implant. J Ophthalmic Inflamm Infect. 2012;2:1-5.
7. Khurana RN, Appa SN, McCannel CA, et al. Dexamethasone implant anterior chamber migration: risk factors, complications, and management strategies. Ophthalmology. 2014;121:67-71.
8. Cronin KM, Govind K, Kurup SK. Late migration of dexamethasone implant into anterior chamber. Arch Ophthalmol. 2012;130:711.
9. Voykov B, Bartz-Schmidt KU. Dislocation of dexamethasone intravitreous implant. Arch Ophthalmol. 2012;130:706.
10. Malcles A, Janin-Manificat H, Yhuel Y, et al. [Anterior chamber migration of intravitreal dexamethasone implant (Ozurdex®) in pseudophakic eyes: Report of three cases.]. J Fr Ophtalmol. 2013;36:362-367.
11. Adan A, Pelegrin L, Rey A, et al. Dexamethasone intravitreal implant for treatment of uveitic persistent cystoid macular edema in vitrectomized patients. Retina. 2013;33:1435-1440.
12. Eadie JA LR, Capone, Jr A. Migration of Ozurdex implant into the anterior chamber. Retinal Cases and Brief Reports. 2012;6:269-270.
13. Vela JI, Crespi J, Andreu D. Repositioning of dexamethasone intravitreal implant (Ozurdex®) migrated into the anterior chamber. Int Ophthalmol. 2012;32:583-584.
14. Kishore SA, Schaal S. Management of anterior chamber dislocation of dexamethasone implant. Ocul Immunol Inflamm. 2013;21:70-71.
15. Marin-Lambies C, Gallego-Pinazo R, Garcia-Delpech S, Diaz-Llopis M. [Ozurdex® and aphakia: a combination to avoid.] Arch Soc Esp Oftalmol. 2012;87:191-192.
16. Laplace O, Rodallec T, Akesbi J, Sandali O. [Anterior chamber migration of a dexamethasone implant in a pseudophakic patient with a scleral-fixated posterior chamber intraocular lens]. J Fr Ophtalmol. 2013;36:e59-61.
17. Collet B. Management of Ozurdex in the anterior chamber. JAMA Ophthalmol. 2013;131:1651-1652.
18. Bratton ML, He YG, Weakley DR. Dexamethasone intravitreal implant (Ozurdex) for the treatment of pediatric uveitis. JAAPOS. 2014;18:110-113.
19. Kocak N, Ozturk T, Karahan E, Kaynak S. Anterior migration of dexamethasone implant in a pseudophakic patient with intact posterior capsule. Indian J Ophthalmol. 2014;62:1086-1088.
20. Mateo C, Alkabes M, Bures-Jelstrup A. Scleral fixation of dexamethasone intravitreal implant (Ozurdex®) in a case of angle-supported lens implantation. International ophthalmology. 2014;34:661-665.
21. Chen WL, Lin CT, Yao CC, et al. In-vitro effects of dexamethasone on cellular proliferation, apoptosis, and Na+-K+-ATPase activity of bovine corneal endothelial cells. Ocul Immunol Inflamm. 2006;14:215-223.
22. Ruiz-Moreno JM, Montero JA, Artola A, Barile S. Anterior chamber transit of triamcinolone after intravitreal injection. Arch Ophthalmol. 2005;123):129-130.
23. Moshfeghi AA, Scott IU, Flynn HW, Jr., Puliafito CA. Pseudohypopyon after intravitreal triamcinolone acetonide injection for cystoid macular edema. Am J Ophthalmol. 2004;138:489-492.
24. Akduman L, Cetin EN, Levy J, Becker MD, Mackensen F, Lim LL. Spontaneous dissociation and dislocation of Retisert pellet. Ocul Immunol Inflamm. 2013;21:87-89.
25. Chang PY, Kresch Z, Samson CM, Gentile RC. Spontaneous dissociation of fluocinolone acetonide sustained release implant (Retisert) with dislocation into the anterior chamber. Ocul Immunol Inflamm. 2014:11:1-4.
26. Stelton CR TJ, Peterson LT, Khurana RN, Yeh S. Surgical management of anterior chamber migration of a dexamethasone intravitreal implant. Ophthalm Surg Lasers Imaging Retina. 2015. Submitted for publication.

Paying for Drugs When the Bill Is Due

Cash forecasting can help manage those high-limit credit cards. ***By Paul Lucas***

Cash is king! Never more than now has this oft-used business cliché been more appropriate for the medical practice administrator—in particular, a vitreoretinal practice administrator. We all deal with stretching the ever-falling reimbursement dollar and controlling overhead, but few medical specialists have had to adapt as quickly to dramatic financial changes as the retinal subspecialty.

With the advent of high cost FDA-approved injectable and implantable pharmaceuticals, and with more on the way, the protocol for managing cash and the related drug inventories must change to ensure adequate cash is available to meet ongoing operating expenses and drug inventory purchases.

To handle the high volume of drug purchases, the typical practice uses a high-limit credit card. These cards have varying terms, of course, but most offer a grace period for payment with no penalty or interest ranging anywhere from seven to 30 days. Online account access lets you readily see future payment obligations and due dates.

A Sword With Two Edges

Complicating this process are the various deferred payment terms the drug manufacturers offer. Depending on the drug, these can range from 30 to more than 100 days. Like any credit scenario, this is a two-edged sword. The lengthy payment terms give the practice the opportunity to use most of its drug inventory before the payment due dates. On the other hand, if the practice does not place controls on cash management, there might not be enough money on hand when the credit card is due.

To ensure this dilemma never arises, the retina practice needs some basic cash forecasting tools. Best practices suggest a weekly projection of cash inflows and outflows for at least three months, although a full-year projection is best. Historical patient volumes and related reimbursements offer the best source for projecting future incomes.

Payroll and payables are easy to account for by reviewing historical financial statements and by breaking down the monthly expenses by week based on invoice-due dates. Drug purchases or, more importantly, the charge date (assuming they're credit card purchase), can be identified by reviewing purchase reports from manufacturers and/or distributors.

Combining these three elements—reimbursement inflows, operating expense outflows and drug purchase payment dates—gives the details you need to forecast cash. Of course, capital purchases and any related debt-service payments must also be considered. However, these transactions are generally planned in advance and can be incorporated into the cash forecast as the group makes purchase approvals.

Retina Group LLC					
Sample Weekly Cash Flow Projection		ACTUAL			FORECAST
	02/02-02/08	02/09-02/15	02/16-02/22	02/23-03/01	03/02-03/08
Beginning Cash Balance	$256,000	$291,507	$272,375	$286,051	$350,482
Patient receipts	132,869	65,423	125,779	108,024	108,024
Loans					
Other receipts	1,200				
Subtotal	134,069	65,423	125,779	108,024	108,024
Available Cash	390,069	356,930	398,154	394,075	458,506
Payroll, Net	18,665		19,241		18,800
Payroll Taxes	10,499		10,985		10,650
Payroll, Other	2,788		2,902		2,800
Subtotal	31,952	0	33,128	0	32,250
Capital Purchases	0	0	0	0	0
Credit Card 1	59,070	71,900	48,450	22,503	73,687
Credit Card 2	1,090	495	20,800	11,361	33,470
Operating Expenses	5,600	10,860	9,725	8,728	8,728
Debt Service	500	575		1,000	
Other outflows	350	725			
Total Outflows	98,562	84,555	112,103	43,592	148,135

This example of a cash forecast spreadsheet shows three weeks of actual revenues and expenses and two weeks of projected.

Bringing Pieces Together

Given the fragmented sources of this critical information, an Excel spreadsheet or something similar can bring all these pieces together so that you can know each week's cash position and plan for it well in advance. Like any forecast, the numbers are only as good as the data entered.

Accordingly, the forecast should be updated at least weekly to remain current as well as provide as much advance notice as possible of any potential "tight" weeks that may lie ahead. I provide an example of just a few weeks of such a spreadsheet or reference.

By updating forecast data to actual numbers over time, the forecast will incorporate prior cash flow into predicted cash flow. With a vigilant eye on the numbers, the practice should find itself in the position to reduce (and hopefully eliminate) any guesswork surrounding cash management.

Mr. Laurita is administrator at Retina Associates of Cleveland Inc. in Ohio.

Mr. Lucas is CFO and administrator of Georgia Retina PC, Atlanta.

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

OCT and FP: Why can't I bill both?

New guidance from CMS describes why and the few times when you can.

Fairly often, questions arise regarding the appropriate coding and billing of fundus photography, CPT 92250, and scanning computerized ophthalmic diagnostic imaging of the retina (SCODI-R), CPT 92134, also called retinal OCT. According to Medicare's National Correct Coding Initiative (NCCI), these codes are considered mutually exclusive when performed on the same date of service; bill just one.

We appreciate that some diagnostic technologies, such as scanning laser ophthalmoscopy (SLO), allow simultaneous capture of a fundus photography (FP) and optical coherence tomography (OCT) image. Choosing the code to submit on a claim for reimbursement requires some careful consideration. New instructions were published in *CPT Assistant* in December 2014 to guide the selection.

Billing Both OCT and FP

In 2000, the NCCI edits bundled the original SCODI code (CPT 92135) with fundus photography (FP) (CPT 92250). In 2011, a new SCODI code, 92134, was bundled with FP, 92250.[1] A bundle means that just one service, usually the higher-reimbursed one, will be reimbursed when both are done on the same day.

However, the NCCI edits are not absolute, and under some circumstances they do allow reimbursement for both services performed on the same day. According to the NCCI edits, the modifier indicator is "1", so it is possible to unbundle SCODI-R and FP using modifier 59, subject to certain limitations.

The *General Correct Coding Policies for NCCI Policy Manual for Medicare Services*[2] discusses the column 1 and column 2 edits in the Mutually Exclusive Edit Table. It states:

> *The CMS developed the NCCI to prevent inappropriate payment of services that should not be reported together … Each edit table contains edits which are pairs of HCPCS/CPT codes that in general should not be reported together. Each edit has a column one and column two HCPCS/CPT code. If a provider reports the two codes of an edit pair, the column two code is denied, and the column one code is eligible for payment. However, if it is clinically appropriate to utilize an NCCI-associated modifier, both the column one and column two codes are eligible for payment.*

Using modifier 59 to break the NCCI edit must be "clinically appropriate".[3] CMS published the Modifier 59 article providing further guidance on this issue. It states:

> *Modifier 59 is used appropriately for different anatomic sites during the same encounter only when procedures which are not ordinarily performed or encountered on the same day are performed on different organs, or different anatomic regions, or in limited situations on different, non-contiguous lesions in different anatomic regions of the same organ.*

It further states: "*Treatment of posterior segment structures in the eye constitutes treatment of a single anatomic site.*" If FP and OCT are done in a single encounter, the use of modifier 59 precludes this guidance. Further, because the posterior segment of the eye is considered a contiguous structure, the guidance rarely supports breaking the NCCI edit.

Coding for SLO

In April 1999, *CPT Assistant* answered a question about proper coding for SLO.[4] It stated:

> *CPT 92135 Scanning computerized ophthalmic diagnostic imaging (eg, scanning laser) with interpretation and report, unilateral, is intended to report a method of objective measuring involving a quantitative determination of the thickness of the retinal nerve fiber layer and computer analysis of the data with the final results of creation of a database file, saving data for further comparing in follow-up examinations. It is not appropriate to assign CPT code 92135 for scanning laser fundus photography. CPT code 92250 Fundus photography with interpretation and report, that describes generation of retinal image only, and not data generation, would be appropriately assigned for this procedure.*

Fifteen years later in 2014, in the context of new technology that expanded the capabilities of SLO, the same question was posed to *CPT Assistant*. The answer, in the November 2014 issue,[5] was different in a subtle and nuanced manner:

> ***Q:*** *Is it appropriate to report CPT code 92135 (now codes 92133 and 92134) for this method of examination of the fundus?*
>
> ***A:*** *If the scanner produces an image of the retina or optic nerve along with other data and imaging for quantitative analysis, it would be appropriate to report a single service from*

the appropriate scanning computerized ophthalmic diagnostic imaging code range (92133-92134). If only an image is obtained then code 92250 would be reported.

It goes on to explain that medical necessity of the FP or OCT service depends on what is needed rather than what is done.

It is important to note that if the only necessary service provided is generating a fundus photograph without the need to quantify the nerve fiber layer thickness and to analyze the data via a computer, then code 92250 is appropriate even if the photograph was taken with a scanning laser.

Pick Just One, But Which One?

When FP and OCT are performed concurrently, some billers routinely choose the test with the highest reimbursement, typically fundus photography, to submit on a claim. In light of the discussion here, that approach is too simplistic and ignores the medical necessity criterion.

The individual condition of the patient is a better starting point when selecting which code to bill; the retina specialist should make the choice rather than depend on the biller to pick the code that represents more dollars.

Conclusion

Advances in ophthalmic imaging, such as SLO, permit simultaneous capture of FP and OCT, but Medicare's NCCI edits permit billing just one CPT code, 92250 or 92134, in most cases.

Old instructions in *CPT Assistant* stipulated that 92250 is the correct code to report SLO. New instructions in December 2014 say it depends on whether qualitative or quantitative information is required for the patient's condition. No single answer suits every situation; one needs to exercise clinical judgment to make an appropriate code selection.

Mr. Mack is a senior consultant with the Corcoran Consulting Group. He is based in Galveston, Texas.

References

1. CMS.gov. NCCI Coding Edits. Version 21.0. Effective January 1, 2015. Available at: http://www.cms.gov/Medicare/Coding/NationalCorrectCodInitEd/NCCI-Coding-Edits.html. Accessed January 20, 2015.
2. CMS.gov. NCCI Policy Manual for Medicare Services. Effective January 1, 2015. Chapter 1. Available at: http://www.cms.gov/Medicare/Coding/NationalCorrectCodInitEd/index.html?redirect=/NationalCorrectCodInitEd/01_overview.asp. Accessed January 20, 2015.
3. CMS.gov. Modifier 59 Article: Proper Usage Regarding Distinct Procedural Service. Updated 10/28/2014. Available at: http://www.cms.gov/Medicare/Coding/NationalCorrectCodInitEd/downloads/modifier59.pdf. Accessed January 20, 2015.
4. Coding Clarification. Medicine Special Ophthalmological Services. American Medical Association. CPT Assistant. April 1999; 10.
5. Coding Clarification. Special Ophthalmological Services (92133, 92134). American Medical Association CPT Assistant. November 2014;10.

Can Anti-VEGF Cause GA in Wet AMD?

(**Literature Review**, *continued from page 14*)

unclear whether the GA that develops in patients undergoing anti-VEGF therapy secondary to neovascular AMD results from macular drying followed by normal disease progression, or whether VEGF inhibition has a neurotoxic effect on the macula, thus causing the more frequent appearance and more rapid growth of GA.

We await the formal publication of the HARBOR Study, in which 2 mg ranibizumab and 0.5 mg ranibizumab were compared using both monthly and PRN regimens. While no data is available on aflibercept and the incidence of GA in the VIEW trials, an ongoing study in Australia comparing ranibizumab and aflibercept to determine whether one causes more GA than the other in neovascular AMD should prove helpful in resolving this question.

As we debate whether anti-VEGF therapy causes GA, there is no question about the efficacy of anti-VEGF therapy for the treatment of MNV in AMD, and we should not withhold treatment. The goal continues to be a dry macula. However, once the macula is dry and GA formation is confirmed, the challenge we have is whether we should consider a less aggressive regimen. This question of anti-VEGF therapy and GA will have particular relevance in the future when sustained-release formulations reach our clinics.

Disclosure: *Dr. Rosenfeld disclosed he is a consultant to Genentech.*

References

1. Brown DM, Kaiser PK, Michels M, Soubrane G, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006, 355:1432-1444.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419-1431.
3. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119:2537-2548.
4. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119:1388-1398.
5. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013;382:1258-1267.
6. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology. 2009;116:57-65 e55.
7. Rosenfeld PJ, Shapiro H, Tuomi L, et al. Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials. Ophthalmology. 2011;118:523-530.
8. Grunwald JE, Daniel E, Huang J, et al. Risk of geographic atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmology. 2014;121:150-161.
9. Grunwald JE, Pistilli M, Ying GS, et al. Growth of geographic atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmology. 2014. Dec. 24. [E pub ahead of print]
10. Xu L, Mrejen S, Jung JJ, et al. Geographic atrophy in patients receiving anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Retina. 2015;35:176-186.
11. Ying GS, Kim BJ, Maguire MG, et al. Sustained visual acuity loss in the comparison of age-related macular degeneration treatments trials. JAMA Ophthalmology. 2014;132:915-921.
12. Tanaka E, Chaikitmongkol V, Bressler SB, Bressler NM. Vision-threatening lesions developing with longer-term follow-up after treatment of neovascular age-related macular degeneration. Ophthalmology. 2015;122:153-161.
13. Channa R, Sophie R, Bagheri S, et al. Regression of choroidal neovascularization results in macular atrophy in anti-vascular endothelial growth factor-treated eyes. Am J Ophthalmol. 2015;159:9-19.
14. Kumar N, Mrejen S, Fung AT, et al. Retinal pigment epithelial cell loss assessed by fundus autofluorescence imaging in neovascular age-related macular degeneration. Ophthalmology. 2013;120:334-341.

By Richard Mark Kirkner »

Selecting Patients for the Iluvien Implant

Sustained-release device emerges after a decade-long journey.

With the shipments of the first supplies of the multi-year, sustained-release implant Iluvien, vitreoretinal surgeon Sanford Chen, MD, acquired another option for patients with diabetic macular edema (DME) who do not completely respond to anti-VEGF therapy. "If you look at the numbers of patients on chronic care, 25 percent or more of them continue to have persistent swelling, and a significant number don't achieve better than 20/40 visual acuity as well," he says.

Iluvien releases submicrogram levels of fluocinolone acetonide to the retina for the treatment of DME. The Food and Drug Administration (FDA) approved Iluvien in September 2014, and Alimera Sciences spent the intervening months building inventory and a sales force, says Dan Myers, Alimera co-founder, president and CEO. Iluvien contains 0.19 mg of fluocinolone acetonide.

When Anti-VEGF Doesn't Work

Dr. Chen, who practices at Orange County Retina in Southern California and is a member of the Fluocinolone Acetonide in Diabetic Macular Edema (FAME) Study Group, says the implant also meets a need for patients who cannot sustain the burden of monthly anti-VEGF therapy. "Patients with diabetes are usually younger and productive members of society," Dr. Chen says.

"They also frequently have other comorbities (such as heart and kidney disease) that require follow-up at other doctors' offices. This may make it difficult for them to come into the office every month for intravitreal anti-VEGF injections," Dr. Chen says.

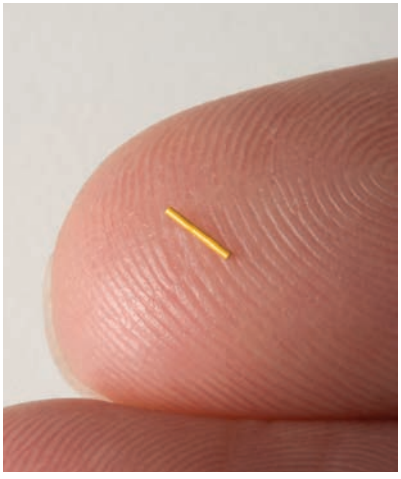
Another population well-suited to the implant may be non-responders or suboptimal responders to anti-VEGF agents, Dr. Chen says. "We know through research that DME is a multifactorial disease and there is probably more than just a VEGF component; there is likely an inflammatory component to it as well," he says.

Patients who have had previous vitrectomy or retina surgery represent a lesser-known group that may benefit from the Iluvien implant. "Having the implant may help in their treatment, because once a patient has had a vitrectomy, the anti-VEGF agent literally can be cleared out in a week," Dr. Chen says. "The pharmacokinetics of the Iluvien implant follows zero-order kinetics and allows for slow release up to 36 months."

An Education Process

FDA approval of Iluvien culminated a decade-long journey that included three prior negative FDA decisions. The journey started in 2004 when Alimera acquired the rights to the implant for delivering steroids to the back of the eye. At the time, Mr. Myers had recently started Alimera, having previously been with Novartis Ophthalmics, where he served as president from 1997 through 2002.

Mr. Myers chalks up the FDA experience as a learning process. "It's the same learning process about diabetic macular edema that the retina community is going through right now," he says. The breakthrough was



The Iluvien implant.

language in the final label indication that required a patient to have had prior steroid treatment with no clinically significant rise in IOP.

"We've learned, as the retina specialists have learned, that DME is more of a multifactorial disease than wet age-related macular degeneration," Mr. Myers says. "Multiple cytokines are involved, and DME has more of an inflammatory aspect than we realized a few years ago."

In 2011, when the FDA issued a critical Complete Response Letter on Iluvien, clinical opinions about the use of steroids in the treatment of DME were just forming. "Maybe the view questioning if a steroid would be necessary for treating DME in 2011 progressed to where we find ourselves today: where there's no question there will be a large number of patients who will need both anti-VEGF therapy and treatment by steroids as well," Mr. Myers says.

Now those patients with DME have a multi-year option.

A Quick Look at CHROMA, SPECTRI

Lead investigator provides details on parallel trials of lampalizumab.

CHROMA and SPECTRI are parallel Phase III trials investigating lampalizumab for the treatment of geographic atrophy (GA) in age-related macular degeneration (AMD). The identically designed, double-masked, randomized studies will compare a 10-mg dose of lampalizumab administered every four or six weeks by intravitreal injection to sham injections. The trials are currently enrolling patients.

The MAHALO Phase IB/II trial preceded SPECTRI and CHROMA. MAHALO was a cohort study of 108 fellow untreated eyes of 143 patients with GA resulting from AMD. Comparing optical coherence tomography images at baseline and 18 months after the start of treatment with lampalizumab, the MAHALO study authors concluded that GA lesions seemed to enlarge at a slower rate in eyes with outer retinal tabulation (ORT) than in eyes without ORT.

Neil B. Bressler, MD, of Wilmer Eye Institute, Baltimore, and chair of the trials' Executive Advisory Committee, answered questions via e-mail about the twin trials.

Q How do CHROMA and SPECTRI differ from the MAHALO phase II trial?

A SPECTRI and CHROMA are Phase III studies being done in parallel, whereas MAHALO was a Phase II study. The Phase II study was designed to determine if it was feasible to proceed with a Phase III trial. The Phase III trials are designed to identify, confidently, if there is a benefit, with acceptable safety, of lampalizumab in the management of geographic atrophy from age-related macular degeneration.

Q What are the primary and secondary endpoints of the twin trials?

A The primary outcome is change in geographic atrophy area from baseline, as assessed by retinal imaging. The key secondary outcomes include change in best-corrected visual acuity from baseline and change in additional measures of visual function.

Q How many centers will participate in the trials?

A Approximately 275 centers are anticipated to enroll study participants across more than 20 countries around the world between CHROMA and SPECTRI.

Q How many patients will ultimately be enrolled?

A SPECTRI and the similarly designed CHROMA trials are anticipated to enroll 936 patients in each study.

Q When will enrollment cease?

A Enrollment likely will cease when the planned sample size of 936 study participants has been attained in each study, assuming enrollment is being completed in a timely fashion and no substantive changes to the protocol are undertaken that might affect this plan.

Q Are the studies accepting any more centers/investigators?

A At this point there are no plans to add new sites to CHROMA-SPECTRI, but there are other studies being planned in GA. Sites can contact Roche (Genentech in the United States) if interested.

Q How would they contact the trial leaders?

A Investigators interested in discussing possible participation in the study can contact Roche (www.roche.com/about_roche/roche_worldwide.htm) and reference Study ID Number: GX29176.

Q When would the earliest Phase III results be available?

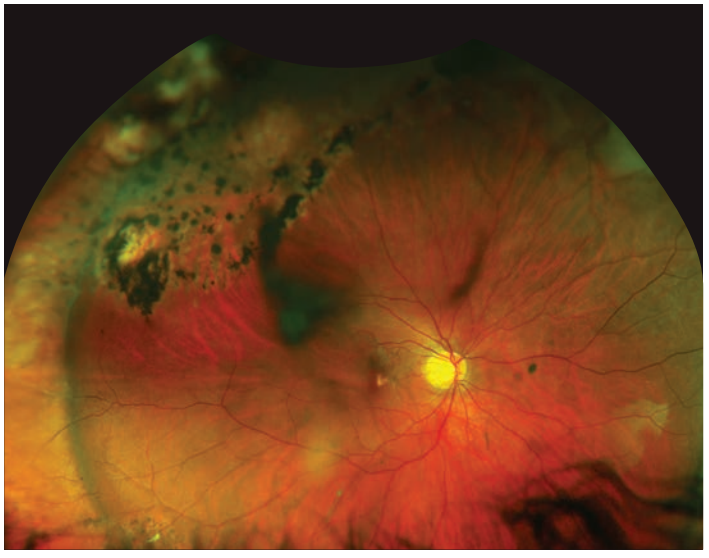
A After the last patient enrolls, that last study participant will reach the primary outcome one year later and complete the last study visit two years later. Additional time, is needed to analyze the data and prepare a report for regulatory authorities. These processes dictate how soon the results would be available.

Long Story Short: CHROMA and SPECTRI

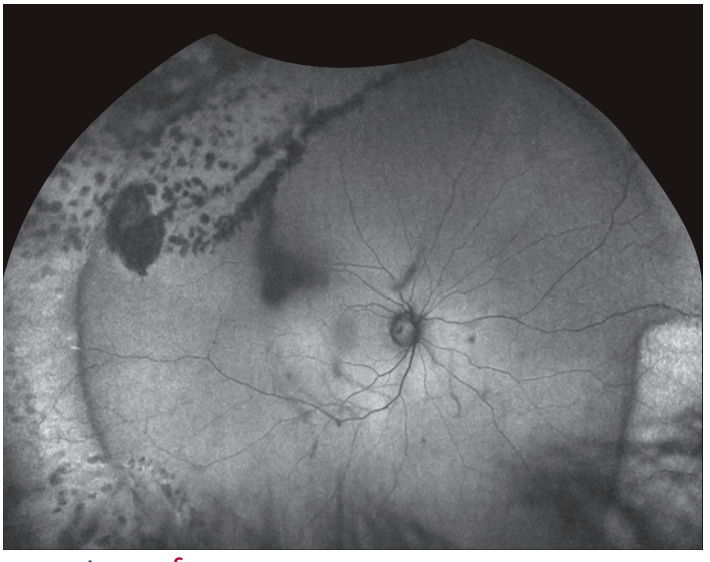
Formal study title: A Study Investigating the Safety and Efficacy of Lampalizumab Intravitreal Injections in Patients With Geographic Atrophy Secondary to Age-Related Macular Degeneration. (SPECTRI and CHROMA share the same title.)

ClinicalTrials.gov Identifiers: SPECTRI, NCT02247531; CHROMA, NCT02247479.

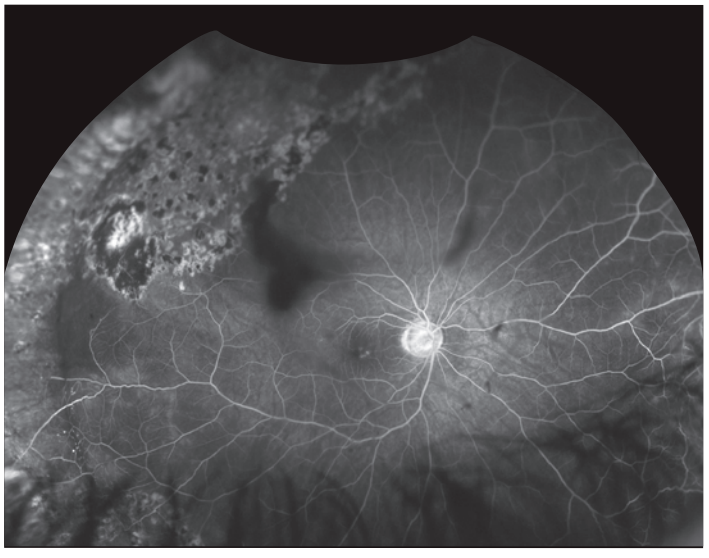
Optos is Ultra-widefield Retinal Imaging



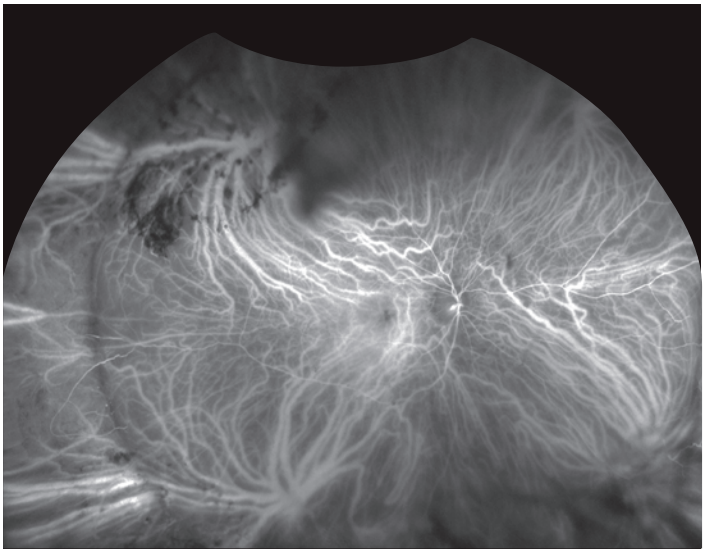
optomap



optomap *af*



optomap *fa*



optomap *icg*

Images courtesy of SriniVas Sadda, MD - Doheny Eye Institute

Optos has the only imaging technology that can capture ultra-widefield images of 200° or 82% of the retina. We have expanded our already extensive variety of imaging modalities with the addition of Indocyanine Green Angiography - **opto**map ***icg***.
See more, discover more, and treat more effectively.

Find out more about what's new from Optos. www.optosnextgen.com

Visit us at ASCRS - **Booth #2708**

optos®

Building *The* Retina Company

The moment you discover visualization that delivers more for retinal assessment.

New CIRRUS HD-OCT Smart Imaging.

NEW!
HD Scan Patterns
En Face Clinical Presets

// SMART OCT
MADE BY ZEISS

Introducing the NEW CIRRUS™ HD-OCT scan patterns and en face clinical presets from ZEISS. Targeted visualization of critical anatomy adds flexibility to your macular assestment while automatic centering improves clinic flow by eliminating rescans due to missed fovea.

- SMART high-definition B-scan automatically centered on the fovea
- En Face clinical presets quickly localize pathology by retinal layer

Discover how the new SMART OCT imaging applications can deliver MORE for your practice.
www.meditec.zeiss.com/cirrus

ZEISS
We make it visible.

Carl Zeiss Meditec, Inc. 800.342.9821 www.meditec.zeiss.com