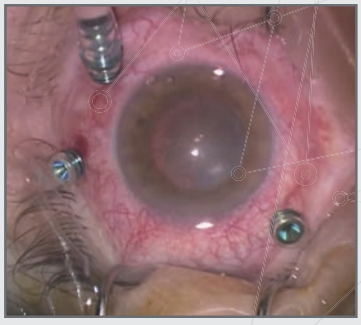
A PUBLICATION BY REVIEW of Ophthalmology

RETINA SPECIALIST

NOVEMBER 2016

Focus on Surgery

3 NOVEL SURGICAL TECHNIQUES … WITH VIDEOS



The Case For Phacovitrectomy

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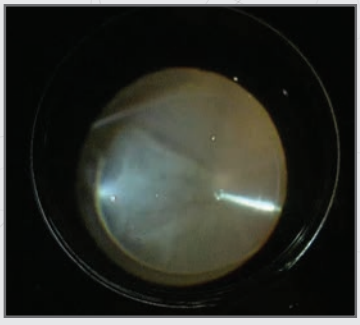
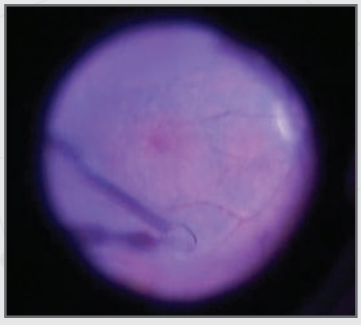


PFO-foscarnet Pocket for RD In Viral Retinitis

PAGE 24



A Simplified Macular Peeling Approach

PAGE 27

ALSO INSIDE:

In DME,* macular edema following RVO,† and noninfectious posterior segment uveitis,

WHEN VISUAL ACUITY STOPS CLIMBING

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

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

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

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.

START EARLY

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

Consider OZURDEX® early, for a pathway toward proven clinical results.

The OZURDEX® approach:

- Achieves clinically significant 3-line gains in BCVA[1,‡]
- Significantly reduces vitreous haze versus sham in noninfectious posterior segment uveitis[1]
- Suppresses inflammation by inhibiting multiple inflammatory cytokines[1]

*Diabetic macular edema. †Retinal vein occlusion. ‡Best-corrected visual acuity.

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions

Diabetic Macular Edema

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

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

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

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

Retinal Vein Occlusion and Posterior Segment Uveitis

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

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

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

1. OZURDEX® Prescribing Information.

Allergan

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.

Rx only

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RETINA SPECIALIST

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Jobson Medical Information LLC

By Charles C. Wykoff, MD, PhD

The Good Fight

When I ask my kids what they want to be when they grow up, I get your typical "dolphin trainer" or "inventor." Nobody wants or expects to be *burnt out*. Unfortunately, about half of physicians are.[1]

There are certainly days that tempt me to go to my knees. The continuous influx of new data and regulatory requirements can be overwhelming. Don't let it be. You and I, retina docs on the front line, are the tip of the sword. We are the real point of care—not the politicians on their stump, the EMR, the newest imposing regulation, the thought of a malpractice suit, or the headache of insurance verifications. Your patients' vision depends on you, in the moment, doing the right thing for them alone. Take a deep, slow breath and tap into that feeling that brought you here in the first place.

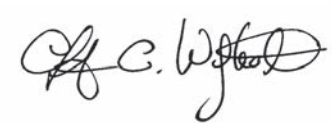
One of the reasons I went into retina is because I love to operate. It is extraordinarily gratifying to care for a patient through necessary surgical intervention. Toward this end, three articles in this "Focus on Surgery" theme issue consider specific facets of retinal surgery:

- "Making the Case for Combined Phacovitrectomy" by Rohit Adyanthaya, MD (*page 20*).
- "A Novel Approach for Retinal Detachment in Viral Retinitis" by David R.P. Almeida, MD, MBA, PhD, and Eric K. Chin, MD (*page 24*).
- "A Simplified Three-Step Approach to Macular Peeling" by Robert A. Sisk, MD (*page 27*).

Another reason I went into retina is the excitement of new discoveries in clinical research. I have considered diabetic retinopathy to be a progressive retinal vascular disease initiated by blood vessel damage and regional hypoxia, with the key clinical manifestations being diabetic macular edema and proliferative diabetic retinopathy.

However, accumulating evidence suggests diabetic neuropathy of the retina may precede the vascular damage we see clinically and histopathologically. Aaron M. Ricca, MD, Elliott H. Sohn, MD, and Michael D. Abramoff, MD, PhD, explore the data behind this possibility with potentially substantial management implications (*page 32*).

Yes, the bureaucratic quagmire of modern medicine can be enough to make anyone want to walk away. But, it is a privilege to care for patients with blinding diseases. Sight is precious above all other senses. We must remind each other and ourselves why we became retina specialists in the first place. Keep up the good fight and support each other to avoid burnout.



1. Shanafelt TD, Hasan O, Dyrbye LN, et al. Changes in burnout and satisfaction with work-life balance in physicians and the general US working population between 2011 and 2014. Mayo Clin Proc. 2015;90:1600-1613.

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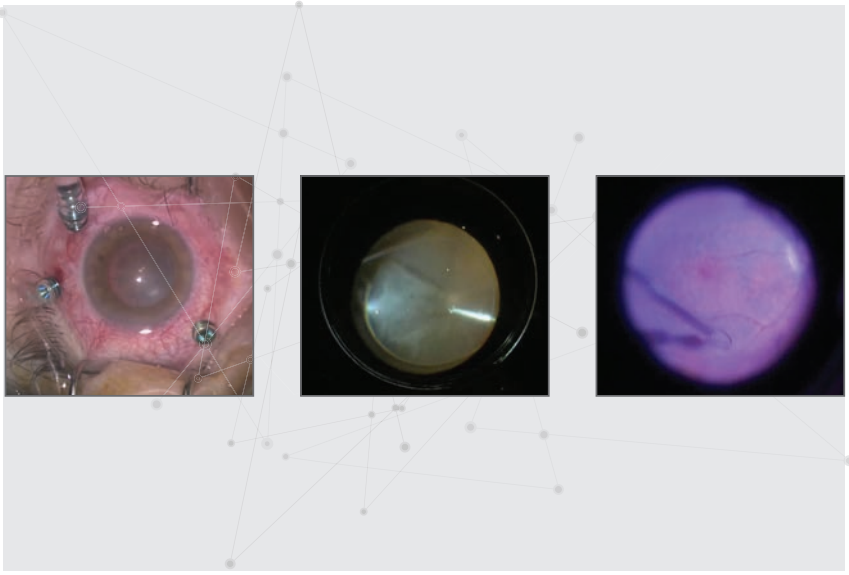

NOVEMBER 2016

FEATURES

Focus on Surgery

DEPARTMENTS

GET READY TO UNITE THE WORLD OF RETINA

INAUGURAL

RETINA WORLD CONGRESS

RETINA WORLD CONGRESS 2017

UNITE. EXCHANGE. ADVANCE.

FEBRUARY 23-26, 2017

FORT LAUDERDALE MARRIOTT
HARBOR BEACH RESORT & SPA
FORT LAUDERDALE, FLORIDA, USA

Retina World Congress (RWC) – An international professional congress that will support global scientific and clinical exchanges on advances in retina health.

REGISTRATION IS NOW OPEN

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This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Global Education Group (Global), MCME Global, and Retina World Congress (RWC). Global is accredited by the ACCME to provide continuing medical education for physicians.

global EDUCATION GROUP | UMA
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M|CME

IN BRIEF

• **Second Sight Medical Products Inc.**, developer of the **Argus II** retinal prosthesis system, announced the first successful implantation and activation of a wireless visual cortical stimulator in a human, providing the initial human proof of concept for the ongoing development of the **Orion Visual Cortical Prosthesis**. Surgeons at UCLA implanted the wireless multichannel neurostimulation system on the visual cortex of the 30-year-old recipient, who then could perceive and localize individual phosphenes with no significant side effects.

• **Applied Genetic Technologies Corporation (AGTC)** filed an investigational new drug application with the U.S. Food and Drug Administration to conduct a Phase I/II clinical trial of its second gene therapy candidate for the treatment of achromatopsia—this one for mutations in the CNGA3 gene. AGTC already has a Phase I/II clinical trial under way of its gene therapy candidate for achromatopsia caused by mutations in the CNGB3 gene. The company plans to initiate the trial of the CNGA3 therapy in the coming months.

• **Genentech** has received FDA approval of the **Lucentis** (ranibizumab) 0.5 mg prefilled syringe for treatment of age-related macular degeneration and macular edema after retinal vein occlusion.

Surgical Robot Performs Macular Peel, Gene Vector Placement

Surgeons at John Radcliffe Hospital in Oxford, U.K., performed the first robotic retina surgery using a Dutch-designed device to accomplish a macular peel in a 70-year-old Anglican priest, and have since used the robot to perform six more operations to place gene vectors in diseased retinas.

The Robotic Retinal Dissection Device—cleverly dubbed R2D2—is the subject of a trial at the University of Oxford involving 12 patients. Macular peels were the first operations retinal surgeons attempted with the robot before accomplishing the fine-needle injections of gene therapy into the retina, Robert E. MacLaren, MBChB, professor at the University of Oxford who conducted the operations, said at the American Academy of Ophthalmology last month in Chicago. The Dutch medical robotics firm Preceyes BV developed the surgical robot and has been working with the University of Oxford's Nuffield Laboratory of Ophthalmology to conduct the clinical trial.

"There is no doubt in my mind that we have just witnessed a vision of eye surgery in the future," Prof. MacLaren said after completing the first macular peel. "Current technology with laser scanners and microscopes allows us to monitor retinal diseases at the microscopic level, but the things we see are beyond the physiological limit of what the human hand can operate on. With a robotic system, we open up a whole new chapter of eye operations that currently cannot be performed."

Robert E. MacLaren, MBChB, conducts the first macular peel using the Robotic Retinal Dissection Device at University of Oxford's John Radcliffe Hospital. ***Credit: University of Oxford***

The robot accesses the surgical area in the eye through a single port less than 1 mm in diameter. It uses seven independent computer-controlled motors to carry out hand movements as precise as 0.001 mm in scale. The surgeon uses a joystick and touchscreen at a control console to manipulate the robotic probe inside the eye, viewing the surgical area through the operating microscope.

The robot can be a breakthrough for delivering gene therapy to the back of the eye, Prof. MacLaren said. "This will help to develop novel surgical treatments for blindness, such as gene therapy and stem cells, which need to be inserted under the retina with a high degree of precision," he said.

The robotics trial follows on Prof. MacLaren's previous work at Oxford in gene therapy for retinitis pigmentosa and age-related macular degeneration.

CONTINUOUS MICRODOSING™ Delivery for Continuous Therapy in Patients With Diabetic Macular Edema (DME)

ILUVIEN is a CONTINUOUS MICRODOSING™ Delivery System specifically engineered for the release of fluocinolone acetonide (FAc) for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

In pivotal studies, ILUVIEN demonstrated a proven increase in visual acuity through 24 months (primary endpoint) and sustained for up to 36 months.[1-3]

Adverse reactions in the ILUVIEN Phase 3 clinical trials were consistent with other corticosteroid treatments.[1]

INDICATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

IMPORTANT SAFETY INFORMATION

Contraindications

- ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

- Intravitreal injections, including those with ILUVIEN, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids including ILUVIEN may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.
- Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions

- In controlled studies, the most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of ≥10 mm Hg (ILUVIEN 34%; sham 10%).

Please see Brief Summary of Full Prescribing Information on reverse side of this page.

1. Iluvien [package insert]. Alpharetta, GA: Alimera Sciences, Inc; 2014. **2.** Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626-635.e2. **3.** Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125-2132.

ILUVIEN®
(fluocinolone acetonide intravitreal implant) 0.19mg

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg For Intravitreal Injection

INDICATIONS AND USAGE

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

CONTRAINDICATIONS

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

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

Hypersensitivity: ILUVIEN 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 **ILUVIEN**, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.

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

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

Clinical Studies 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 the clinical trials of another drug and may not reflect the rates observed in practice.

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

ILUVIEN was studied in two multicenter, randomized, sham-controlled, masked trials in which patients with diabetic macular edema were treated with either **ILUVIEN** (n=375) or sham (n=185). Table 1 summarizes safety data available when the last subject completed the last 36-month follow up visit for the two primary **ILUVIEN** trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three-year follow up period, approximately 75% of the **ILUVIEN** treated subjects received only one **ILUVIEN** implant.

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

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Cataract[1]	192/235[2] (82%)	61/121[2] (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)

Table 1 (continued)

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

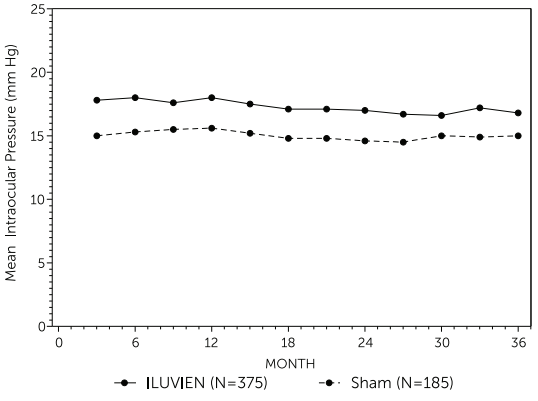
[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
IOP elevation ≥ 10 mm Hg from baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mm Hg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

At baseline, 235 of the 375 **ILUVIEN** subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **ILUVIEN** group (82%) compared with sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the **ILUVIEN** group and 19 months in the sham group. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both **ILUVIEN** group and for sham) of the studies.

Postmarketing Experience: The following reactions have been identified during post-marketing use of **ILUVIEN** in clinical practice. Because they are reported voluntarily, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ILUVIEN**, or a combination of these factors, include reports of drug administration error and reports of the drug being ineffective.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.
There are no adequate and well-controlled studies of **ILUVIEN** in pregnant women. Animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. **ILUVIEN** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with **ILUVIEN** is low. It is not known whether intravitreal treatment with **ILUVIEN** could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when **ILUVIEN** is administered to a nursing woman.
Pediatric Use: Safety and effectiveness of **ILUVIEN** in pediatric patients have not been established.
Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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ALIMERA SCIENCES

Vector Gene Transfer for NVAMD Sustains Expression Up to 4 Years

A Phase I trial of a vector gene transfer to treat advanced wet age-related macular degeneration demonstrated reproducible, sustained transgene of two therapeutic proteins that block neovascularization expression for at least 2.5 years.[1]

The study evaluated the lentiviral Equine Infectious Anemia Virus (EIAV) vector RetinoStat (Oxford BioMedica, Oxford, U.K.), engineered to deliver the therapeutic genes endostatin and angiostatin, each of which blocks the neovascularization characteristic of progressing neovascular AMD. Twenty-one study participants received a subretinal injection of either 2.4×105 TU or 8.0×105 TU of the viral vector in one eye. Previous study results reported the vector gene had a favorable safety and tolerability profile.

The study patients had highly fibrotic retinas and had become non-responsive to anti-VEGF therapy after having a history of response. The study showed that therapeutic gene expression, a secondary endpoint of the trial, was dose-dependent and maintained for 2.5 years in eight subjects and more than four years in two.

Mean levels of endostatin and angiostatin, measured in the aqueous humor, peaked between weeks 12 and 24 at 57 to 81 ng/mL for endostatin and 15 to 27 ng/mL for angiostatin, and remained stable through the last measurement at week 48. Long-term follow-up demonstrated the longer durations for expression.

The study reported no dose-limiting toxicities and little or no ocular inflammation. The investigators did report one procedure-related serious adverse event, a macular hole, which resolved.

"Despite an apparent reduction in fluorescein angiographic leakage that broadly correlated with the expression levels in the majority of patients, only one subject showed convincing evidence of anti-permeability activity in these late-stage patients," said the investigators, led by Peter A. Campochiaro, MD, of the Wilmer Eye Institute at Johns Hopkins University in Baltimore.

Patients who received the 8.0×105 TU injection demonstrated no significant change in mean lesion size.

"These data demonstrate that EIAV vectors provide a safe platform with robust and sustained transgene expression for ocular gene therapy," Dr. Campochiaro and co-authors said.

Other study investigators were Andreas K. Lauer of the Oregon Health Sciences Center at the University of Oregon and Elliott H. Sohn, MD, of the University of Iowa.

Dr. Lauer disclosed he is a consultant for Oxford BioMedica. Six co-authors are either former or current employees of BioMedica. Drs. Campochiaro and Sohn and co-author Tahreem A. Mir, MD, had no conflicts to disclose.

REFERENCE

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By Abed Namavari, MD, and Philip J. Rosenfeld, MD, PhD

A Common Masquerade in AMD

The challenge of managing non-vascularized retinal pigment epithelial detachments.

The irreversible loss of vision in late stage age-related macular degeneration is associated with fovea-involving geographic atrophy and macular neovascularization.[1] No treatment currently exists to slow the progression of geographic atrophy, but anti-VEGF agents can effectively treat neovascular AMD.[2]

These patients may need injections as frequently as every month to eliminate the macular fluid and avoid the consequences of inadequately treating macular neovascularization (MNV), which include irreversible vision loss from macular hemorrhages and scar formation. While this fluid can reside within the retina, under the retina and under the retinal pigment epithelium, the most challenging fluid to treat is that below the RPE that presents as a retinal pigment epithelial detachment (PED).[3]

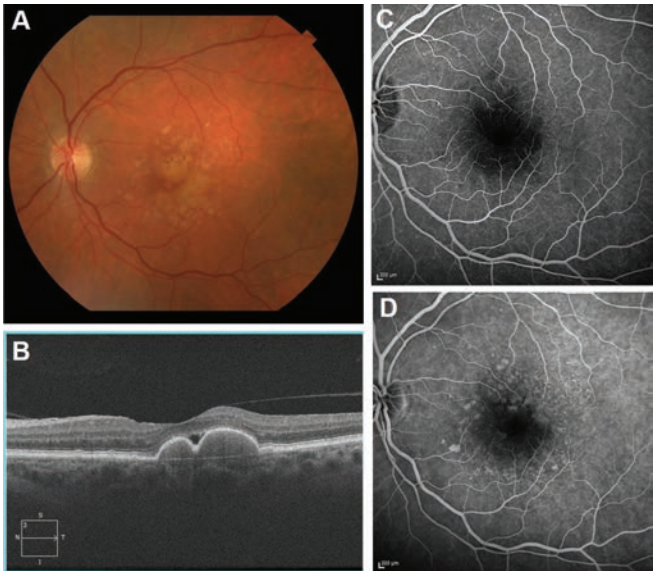

Figure 1. Color fundus photograph of the left eye (A) shows confluent soft drusen. Spectral-domain optical coherence tomography through the fovea (B) shows two adjacent drusen with overlying subretinal fluid between their peaks. Early (C) and late (D) fluorescein angiography show no leakage.

Where ICGA is Helpful

In the past, we depended on fluorescein and indocyanine green angiography to identify and characterize these neovascular lesions, but over the past decade, optical coherence tomography has emerged as the principal imaging technique for patients with neovascular AMD.[4]

While OCT imaging can identify macular fluid in the different anatomic compartments of the macula and monitor fluid response to anti-VEGF therapy, at times it can be difficult to distinguish between macular fluid arising from neovascularization and that arising as a manifestation of non-vascularized AMD, such as subretinal fluid within the valley between drusen[5] and the sub-RPE fluid that forms serous non-vascularized PEDs, which can also include pockets of subretinal fluid at the apex of the PED.[6]

ICGA can be helpful in identifying the neovascularization in PED if it exists.[1] Often, type 1 neovascularization can be identified at the edge of the PED, or within a notch at the edge of the PED, and type 3 neovascularization can appear as a hot-spot within the retina on top of the PED. These type 3 lesions are usually also associated with intra-retinal fluid overlying the PED as well. But, what about those serous PEDs in which no neovascular lesion is obvious on angiography?

If the neovascular lesion is present but not detected using dye-based or OCT angiography, then the consequences of not treating could be catastrophic. Enlarging PEDs can contribute to RPE tears resulting in significant vision loss from submacular hemorrhage. Clinicians often err on the side of caution and treat these lesions because they could be vision-threatening, only to find out later that the PED and associated subretinal fluid are refractory to therapy.

Characteristics Of Non-vascularization

Over the years, we have identified some characteristic features on OCT that suggest when drusenoid or serous PEDs are not vascularized. If anti-VEGF therapy is initiated in the setting of a suspected non-vascularized lesion, and the fluid appears unresponsive to therapy, then it is perfectly reasonable to inject the patient and perform OCT imaging one-to-two weeks later, when the treatment response should be maximal, to look for a response.

If no response is seen, then the fluid probably is not dependent on vascular endothelial growth factor. If

a response does occur, then the lesion is probably in an environment with an overabundance of VEGF, and monthly therapy is just inadequate to suppress the exudation.

Another strategy to use when the lesion appears unresponsive to anti-VEGF therapy, but the clinician is uncomfortable withdrawing therapy, is to slowly extend the interval and follow the lesion with OCT to determine if more fluid accumulates. The cases here demonstrate these management dilemmas.

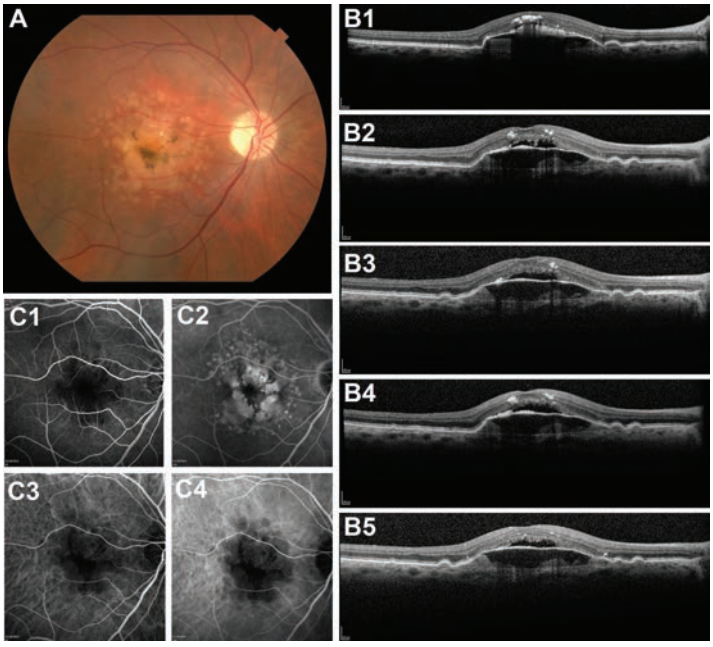

Figure 2. Fundus photography of the right eye (A) reveals confluent drusen, pigment and a pigment epithelial detachment (PED). Spectral-domain optical coherence tomography imaging (B1–B5) through the fovea at baseline, at month two, four, six and eight, respectively, shows predominantly serous PED with overlying subretinal fluid. The subretinal fluid overlying the PED remains relatively unchanged despite monthly aflibercept injections. Early (C1) and late (C2) fluorescein angiography and early (C3) and late (C4) indocyanine green angiography images show no leakage, hot spots or plaques.

Drusen, No Sign Of MNV

A 69-year-old woman was referred for a second opinion. She was originally diagnosed with neovascular AMD in the left eye and had received multiple anti-VEGF intravitreal injections, the last about six weeks before her visit. Visual acuity was 20/25 in the left eye, and a fundus exam revealed confluent soft drusen (*Figure 1*).

SD-OCT imaging of the left eye showed two large drusen with subretinal fluid in between their peaks. However, FA did not show any leakage or sign of MNV. We made the decision to observe with serial SD-OCT imaging, and the subretinal fluid remained stable.

Non-vascularized Serous PED

A 72-year-old man presented with blurred vision in his right eye. VA was 20/100 in the eye. A fundus exam revealed confluent drusen, pigment and a PED (*Figure 2*). SD-OCT imaging revealed a predominantly serous PED with overlying subretinal fluid.

He received monthly injections of aflibercept (Eylea, Regeneron) for the next seven months, during which the SD-OCT findings and VA remained unchanged. FA and ICGA did not show any sign of MNV. We stopped treatment and the lesion remained unchanged.

This lesion is characteristic of a non-vascularized, predominantly serous PED in AMD. Over time, these lesions will collapse into GA.

Overlying Subretinal Fluid

An 81-year-old woman, who was being followed for dry AMD in both eyes, presented with decreased vision in the left eye. VA was 20/30 in that eye. A fundus exam revealed a central PED with adjacent drusen (*Figure 3, page 45*). SD-OCT showed a predominantly serous PED with overlying subretinal fluid.

She received 13 aflibercept injections in that eye over the next 26 months with intervals ranging from four to 14 weeks. The size of the PED and its overlying subretinal fluid remained unchanged at each visit. SD-OCT angiography did not reveal any evidence of neovascularization. Her visual acuity remained at 20/30 during the course of treatment.

'Dry' AMD a Misnomer?

These cases are all examples of subretinal fluid and drusen or PEDs in non-vascularized ("dry") AMD unresponsive to anti-VEGF therapy. The question that arises in all of them is what is the source of the fluid in these lesions. The subretinal fluid is most likely the result of dysfunction of the RPE and its inability to pump fluid from the retina; the serous PEDs likely result from the fluid being pumped

(Continued on page 45)

A Scotoma the Shape of Australia

Does this patient have a white dot syndrome?

By Ariel Tyring, MD, and Kaivon Pakzad-Vaezi, MD

A 55-year-old Caucasian male presented to the University of Washington Eye Institute with complaints of central scotoma in the left eye for three months. The gray scotoma initially appeared as a small round spot and progressed in size until it resembled the "shape of Australia." He had a small central island of preserved vision and reported daily flashing lights.

The patient's ocular history was unremarkable and he was using no eye medications. His medical history included controlled systemic hypertension and hypercholesterolemia. A review of systems was notably negative for weight changes, night sweats, fatigue or foreign travel.

Examination

Best-corrected visual acuity was 20/15-1 and 20/70-1, with intraocular pressures of 13 mmHg and 15 mmHg in the right and left eyes, respectively. A trace afferent pupillary defect was present in the left eye. Extraocular muscle motility and confrontational visual fields were full in both eyes. No anterior chamber or anterior vitreous cells were visible on anterior segment exam.

Dilated fundus exam was unremarkable in the right eye but the left eye showed a 5-disc-area placoid lesion of RPE atrophy in the central macula with a small round hypopigmented lesion along the inferotemporal arcade (*Figure 1A*). No Vascular sheathing, hemorrhages or subretinal fluid were present.

Workup and Diagnosis

Fluorescein angiography of the left eye (*Figures 1B and C*) was notable for early hypofluorescence of the lesion with hyperfluorescent borders. We also noted late staining of the lesion with central mottling.

Fundus autofluorescence showed a hyperautofluorescent lesion with hypoautofluorescent borders (*Figure 2B*). Indocyanine green angiography showed early and late hypoperfusion with loss of choriocapillaris in the central macula corresponding to the lesion (*Figures 2C and D*). Spectral-domain optical coherence tomography revealed well-demarcated outer retinal and RPE loss corresponding to the lesion without cystoid macular edema or choroidal neovascularization (*Figure 2E*).

The laboratory workup included a complete blood count, which was normal, and a complete metabolic panel. HIV antibodies, syphilis titers and quantiferon gold testing were negative. Given the serpiginous appearance of the central placoid lesion with a negative infectious workup and characteristic features, including early hypofluorescence and late hyperfluorescence on FA and hyperautoflorescence on FAF, we diagnosed macular serpiginous choroiditis.

Treatment Plan

We initiated a trial of systemic corticosteroids with prednisone

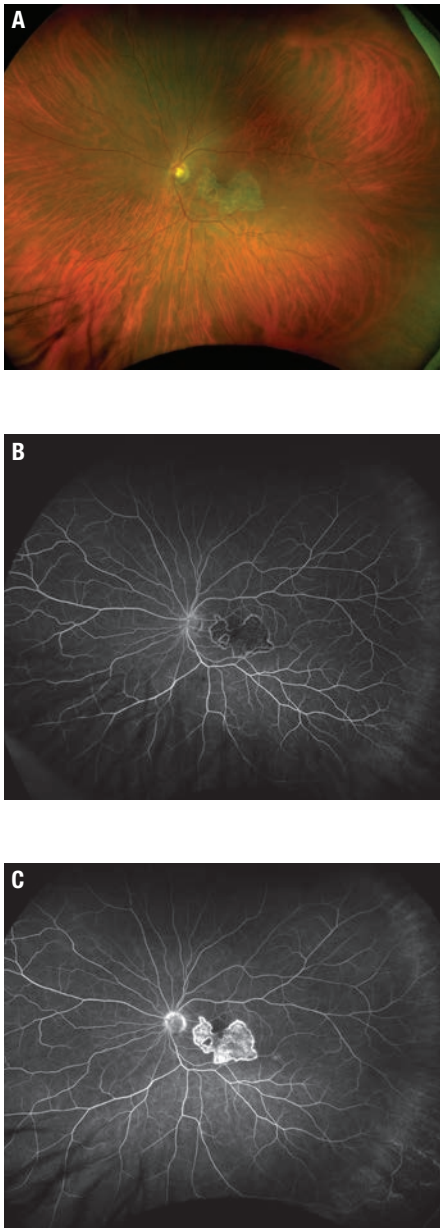

Figure 1. Fundus photograph (A) shows a placoid lesion of retinal pigment epithelium atrophy in the central macula. Early phase fluorescein angiography (B) shows hypofluorescence at the site of the lesion and late-phase FA (C) shows staining.

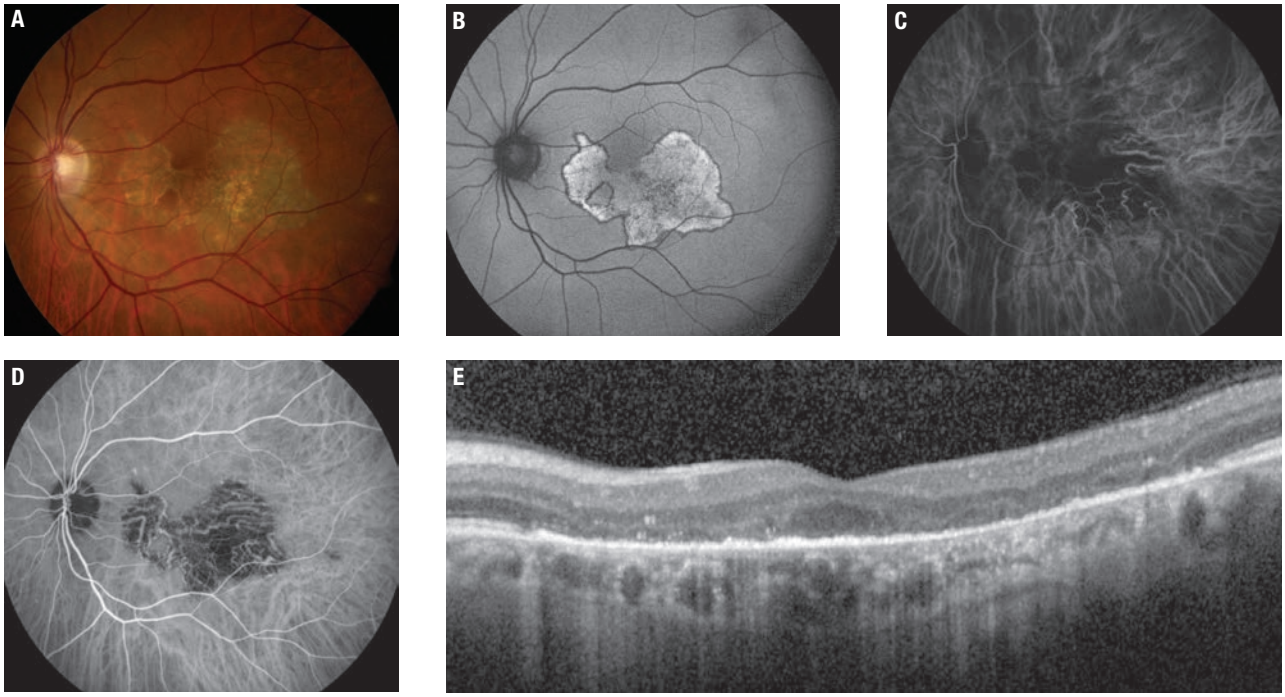

Figure 2. Fundus photograph of the macula (A) shows the placoid lesion while fundus autofluorescence (B) shows a hyperautofluorescent lesion with patchy central hypoautofluorescence. Early indocyanine green angiography (ICGA) (C) exhibits hypofluorescence and late ICGA (D) demonstrates hypofluorescence. Optical coherence tomography (E) reveals outer retinal and retinal pigment epithelium loss without cystoid macular edema or choroidal neovascular membrane.

60 mg daily. At a follow-up examination two weeks later, the patient noted subjective improvement in central scotoma size. On clinical exam we observed a stable lesion appearance, also evident on repeat FAF and FA imaging. Given the concerning finding of hyperautofluorescence of the lesion with risk of disease progression and fellow-eye involvement, we decided to initiate immunomodulatory therapy with mycophenolate mofetil and slowly taper the systemic corticosteroids.

Discussion

Serpiginous choroiditis (SC) is a chronic, asymmetrically bilateral inflammatory posterior uveitis and one of the white dot syndromes. It is characterized by recurrent inflammation of the outer retina, RPE and choriocapillaris.[1] Serpiginous choroiditis typically presents in the fourth to sixth decade of life and affects men more than women.[1-3] It is thought to be a rare condition. While actual prevalence in the United States is unknown, an epidemiologic study in India found SC in up to 18 percent of uveitis referrals.[4]

Patients often complain of decreased vision, central scotoma and metamorphopsia. Lesions classically appear in a peripapillary distribution and extend in a serpentine pattern throughout the posterior pole. Minimal associated vitritis, vasculitis or anterior segment inflammation is present. Initially active lesions are yellowish-gray and, when left untreated, can progress to choroidal and RPE atrophy with mottled pigmentary changes.[1-3.]

While the underlying etiology of SC remains elusive, autoimmune, vascular and infectious causes are implicated. *Mycobacterium tuberculosis* is a well-recognized entity that produces serpiginous-like choroiditis. In fact, studies have shown an association between positive tuberculin skin test and SC, which may indicate a common underling infectious etiology.

Literature from TB-endemic areas has reported clinical characteristics of this TB-related "serpiginous-like choroiditis," or "multifocal serpiginoid choroiditis" to better distinguish it from more classic SC. These characteristics include a greater preponderance of

vitreous inflammation, lesions of a more multifocal pattern or that favor the macula rather than the peripapillary region early on, and a positive response to a full course of antitubercular treatment (ATT).

In these retrospective studies, treatment response to ATT would occur in some cases with or without concomitant corticosteroid therapy, and often without the use of immunosuppression.[5,6] As such, the exclusion of TB is recommended in every case due to the significantly different treatment approaches.

The diagnosis is clinical. However, an investigative workup is mandatory to rule out infectious SC-mimicking conditions such as TB, sarcoidosis, syphilis and herpetic infection.

Imaging studies are helpful to establish diagnosis, determine activity and evaluate response to treatment. FAF is variable and often shows hyperautofluorescent borders adjacent to a helicoid hypoautofluorescent scar.[3] Autofluorescence tends to diminish with decreasing disease activity. FA shows hypofluorescence in early phases followed by progressive late leakage and staining in active lesions (*Figure 1, page 16*). ICGA shows early and late hypofluorescence (*Figure 2, page 17*) representing loss of choriocapillaris. OCT shows hyper-reflective foci associated with disruption of the outer retina and RPE.[1-3]

Other Forms of SC

Besides the classic peripapillary form of SC, two other important clinical variants exist. Ampiginous choroiditis, also referred to as persistent placoid chorioretinitis, represents a hybrid between acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and SC.[7] Lesions are multifocal and occur in both the posterior pole and periphery, but unlike APMPPE the pigment changes and RPE atrophy remain after lesions resolve.[1,8]

Quotable

Because serpiginous choroiditis is almost always a bilateral and progressive disease, addition of immunomodulatory agents can result in better long-term control.

With the macular serpiginous variant, as reflected by the name, the lesions preferentially occur in the macula and may not involve the juxtapapillary retina. Characteristics of this variant are a worse prognosis due to foveal involvement, a destructive course and high frequency of choroidal neovascular membrane formation.[2,3] Because the lesion we describe here exclusively involves the central macula, this is a case of the macular serpiginous variant.

Other important entities in the differential include APMPPE, serpiginous-like tubercular choroiditis, multifocal choroiditis with panuveitis and syphilitic choroiditis. APMPPE is usually self-limiting without sequelae. Significant vitritis characterizes MCP. Complete systemic evaluation can exclude tuberculosis and syphilis.[3]

Treatment is usually initiated with systemic corticosteroids with or without topical or periocular steroids. Because SC is almost always a bilateral and progressive disease, addition of immunomodulatory agents results in better long-term control. Antimetabolites and/or T-cell inhibitors are effective for suppressing the inflammation SC causes. For recalcitrant disease, alkylating agents and biologics can be employed.[3,9] Long-term follow-up is important to monitor response to treatment and detect recurrences. RS

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By Paul Hahn, MD, PhD »

A Heads-up, 3D View on Surgery

Trying out a new digital surgical microscope. ***With Bozho Todorich, MD, PhD, Aristomenis Thanos, MD, Alan J. Ruby, MD, and George A. Williams, MD***

A basic premise for successful surgery is to maintain an optimized view, a capability that often defines the difference between experienced and young surgeons. Although the advanced optics of current surgical microscopes provide a clear view, digitalization may provide enhanced surgical visualization as it has for photography and other fields.

The NGENUITY 3D system for vitreoretinal surgery (Alcon, Fort Worth, Texas), consists of a 4,000-pixel display with an ultrafast, high-definition digital camera that allows for high-resolution, three-dimensional viewing in the operating room. At Associated Retinal Consultants in Royal Oak, Mich., Bozho Todorich, MD, PhD, Aristomenis Thanos, MD, Alan J. Ruby, MD, and George A. Williams, MD, have used this system for over six months and have transitioned to its exclusive use for vitreoretinal cases. In this pearl they share the advantages and limitations of this device for routine use. (The online video available at: bit.ly/2edaYUf)

Four Potential Benefits

In the operating room, here is how NGENUITY 3D performs in these key areas:

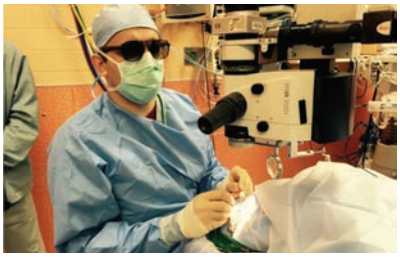
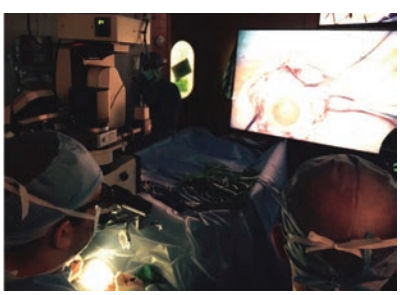


Figure 1. The NGENUITY 3D visualization system can allow the surgeon to view the surgical field while sitting upright rather than stooping over the optics of a traditional surgical microscope.

• ***Surgeon ergonomics.*** An American Academy of Ophthalmology survey noted high prevalence of neck, upper- and lower-extremity pain in 52 percent of surveyed physicians. Operating with NGENUITY has allowed a more ergonomic posture during surgery (*Figure 1*), resulting in noticeably less back pain and fatigue at the end of longer operating days.

• ***Assistant visualization.*** The traditional assistant scope commonly provides a view inferior to the surgeon's scope. The NGENUITY 3D display eliminates this disparity, offering the same view to the surgeon and the assistant at all times. This enhances the surgeon's ability to direct and teach surgical staff and trainees, and improves the quality of recorded surgical videos (*Figure 2*).



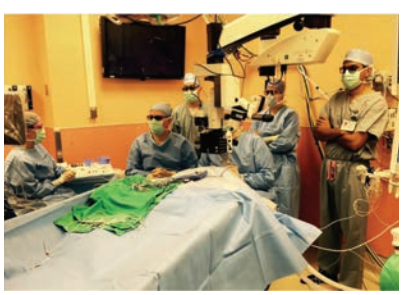


Figure 2. Enhanced viewing with 3D spectacles (left) allows both the surgeon and the assistant to have the same view of the surgical field, which aids in training of vitreoretinal fellows, and surgical staff and observers can have the same view as the surgeon (right) and participate in discussion during the operation.

• ***View and stereopsis.*** NGENUITY 3D augments depth perception, which is particularly helpful during macular surgery and difficult diabetic dissections where axial identification of fine planes is paramount. The NGENUITY 3D camera can also digitally amplify the recorded signal to reduce endoillumination while maintaining sufficient visualization. Decreased endoillumination during macular cases may reduce the risk for photoxicity and also minimizes glare during the fluid-air exchange.

• ***Intraoperative imaging integration.*** NGENUITY 3D has the ability to project preoperative imaging such as optical coherence tomography scans and fluorescein angiograms on the display screen during any portion of the operation. This creates a digital platform to enable multimodal surgeon interaction and, possibly, future integration with intraoperative OCT technology, among other potential capabilities.

Potential Limitations

Some limitations of this technology include the cost of acquisition and initial learning curve. Although the surgeons at Associated Retinal Consultants found the adaptation for posterior segment surgery to be rapid, the hyperstereo of the digital camera made anterior segment surgery and external maneuvers, such as conjunctival closure, initially more difficult.

Also, the ideal position for the

(Continued on page 45)

Focus on Surgery

MAKING THE CASE FOR COMBINED PHACOVITRECTOMY

Performing phacoemulsification and vitrectomy in one procedure makes sense for the surgeon and patient. **By Rohit Adyanthaya, MD**

Techniques and technologies for both cataract and vitrectomy surgery have evolved tremendously in recent years, resulting in improved outcomes and shorter operating times. Cataract surgery is typically performed via a clear-corneal incision ranging in size from 1.5 to 2.8 mm. Similarly, pars plana vitrectomy has been performed safely using progressively smaller instrumentation, including 23, 25 and 27 gauges.[1-5]

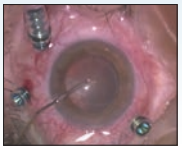
Given the improved safety, speed and recovery time seen with these surgeries, it is apparent that, when done appropriately, combining phacoemulsification and vitrectomy is in the best interests of the patient. This article highlights some of the indications, surgical techniques, advantages and disadvantages of phacovitrectomy when the retina surgeon performs it.

Indications

Patients with visually significant cataracts undergoing vitrectomy are candidates for phacovitrectomy. Even patients with mild degrees of lenticular change are suitable for this procedure, because it will negate their need for inevitable cataract surgery later on and provide excellent posterior pole visualization for the surgeon.

A relative contraindication is a retina surgeon who is inexperienced in phacoemulsification, because prolonged phacoemulsification can lead to corneal edema and poor visualization of the retina during vitrectomy.

However, with existing machines, techniques and viscoelastic devices, phacoemulsification with intraocular lens implantation can be safely performed in 10 minutes without corneal decompensation.



View the Video

Dr. Adyanthaya narrates a video on the key steps of phacovitrectomy in the case of a high myope with a history of a rhegmatogenous retinal detachment who developed a full-thickness retinal hole with a cataract. Available at: bit.ly/2ebmjSa.

Phacovitrectomy Advantages

Phacovitrectomy provides a number of advantages to both the patient and the retina specialist. The patient avoids two trips to the operating room and has a faster overall postoperative recovery course compared with undergoing two separate procedures at different dates. This saves the patient money by avoiding copayments for the second procedure. The patient who does not have health insurance or who otherwise pays out of pocket greatly benefits from the combined procedure. It

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Dr. Adyanthaya is an attending vitreoretinal surgeon at Valley Retina Institute, McAllen, Texas.

DISCLOSURES: Dr. Adyanthaya has no relevant financial disclosures.

also saves the patient time because he or she does not need to make appointments to see an anterior segment surgeon for the cataract procedure. Visual rehabilitation is faster.

For the retina surgeon, advantages include the following:

- Thorough and safe shaving of the vitreous base is possible without fear of lenticular touch.
- It affords a better view of the retina for delicate maneuvers such as internal limiting membrane peeling and for detection of small retinal breaks.
- Posterior capsular rupture or lens drop is less of a concern, because the retina surgeon has the ability to address such issues immediately if they occur.
- Phacoemulsification is easier in a non-vitrectomized eye, because after vitrectomy, cataracts tend to be harder and the anterior chamber tends to fluctuate during phacoemulsification due to the absence of vitreous support, possibly leading to posterior-capsule rents and dropped nuclear fragments. For these reasons, anterior segment surgeons are not keen to operate on vitrectomized eyes.
- There are no scheduling mishaps causing the retina surgeon to have to wait for the cataract surgeon to begin the case.
- Most third-party payers reimburse 100 percent for the retina procedure and 50 percent for the phacoemulsification, which can be an increased source of revenue for the retina surgeon.
- The patient is happy with the retina surgeon's results, rather than allowing the cataract surgeon to become the hero when he or she does the phacoemulsification later.

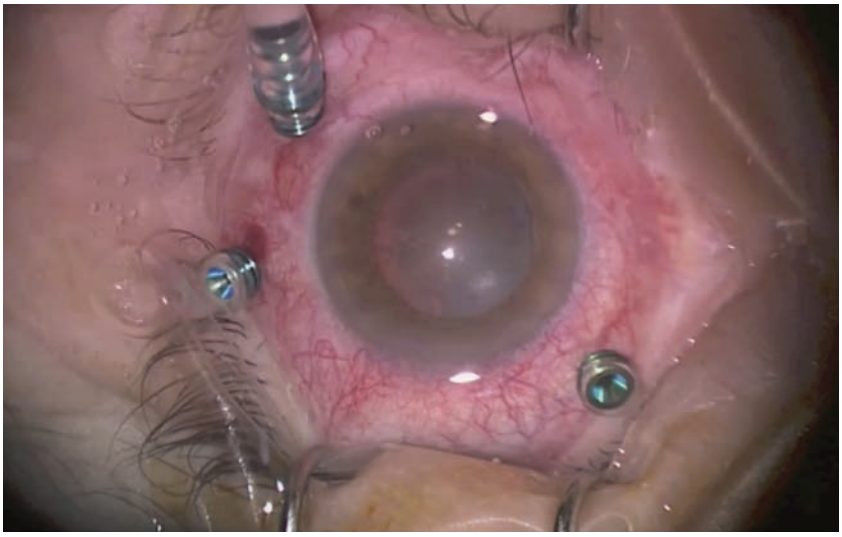

Figure 1. We insert all three ports before starting phacoemulsification because inserting the ports after phacoemulsification creates a slightly higher risk of the main cataract incision gaping due to the pressure applied for port insertion.

- Many ophthalmic manufacturers offer combined packs for phacovitrectomy at almost the same rates as individual phaco packs.
- The U.S. health-care system also stands to benefit from cost savings if retina surgeons perform more phacovitrectomies.[3]

But There are Disadvantages

The retina specialist must also consider several potential disadvantages of combined phacovitrectomy. For example, the retina surgeon may fear a loss of referrals from anterior segment colleagues, although our experience has been quite the opposite. As noted, cataract surgeons like to avoid doing phacoemulsification in vitrectomized eyes due to the higher risk of complications, and they are happy to let us take care of their patients' cataracts during the vitrectomy procedure. Referrals stop, however, when the retina surgeon starts doing primary cataract surgeries.

Another potential disadvantage is that the retina surgeon must be experienced with phacoemulsification. There is also a slightly higher chance of anterior segment inflammation when phacovitrectomy is performed in eyes with diabetic tractional retinal detachment. In such cases, our practice prescribes steroid drops every two hours for the first week rather than the usual four times daily.

Surgery Prep and Techniques

Phacovitrectomy does require some considerations that may be out of the norm for most retina

Take-home Point

Many of our international ophthalmology colleagues have adopted phacovitrectomy as the standard surgical approach for patients with cataract and retinal pathology. In the United States, we foresee a time when third-party payers will prefer retina surgeons who can manage both cataract and retina issues due to the potential for increased benefits to patients and the health-care system.

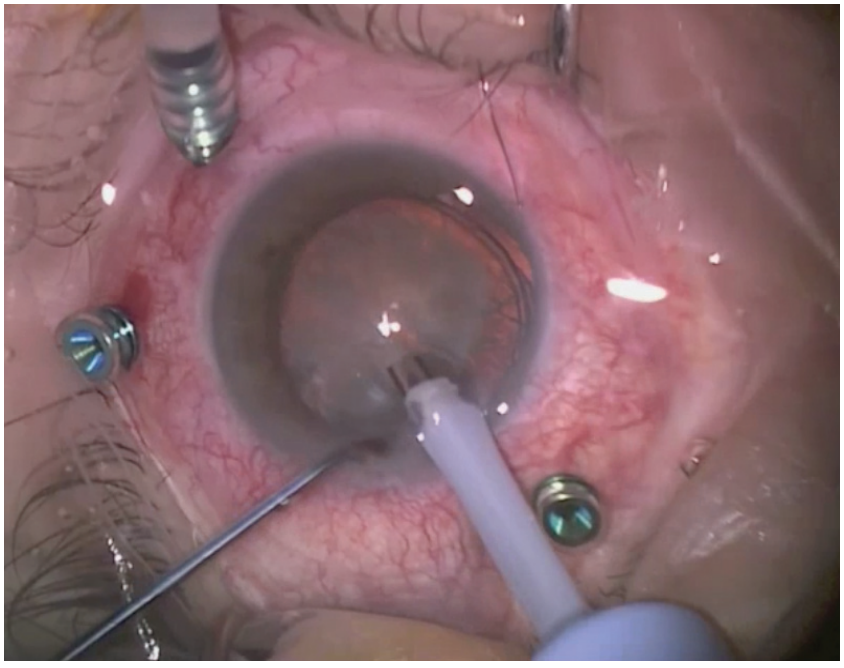

Figure 2. After the capsulorhexis, the phaco needle is introduced with the infusion on. The horizontal chop technique is used to break up the nucleus. Using the chopper and needle, the nucleus is cracked without using any ultrasound energy.

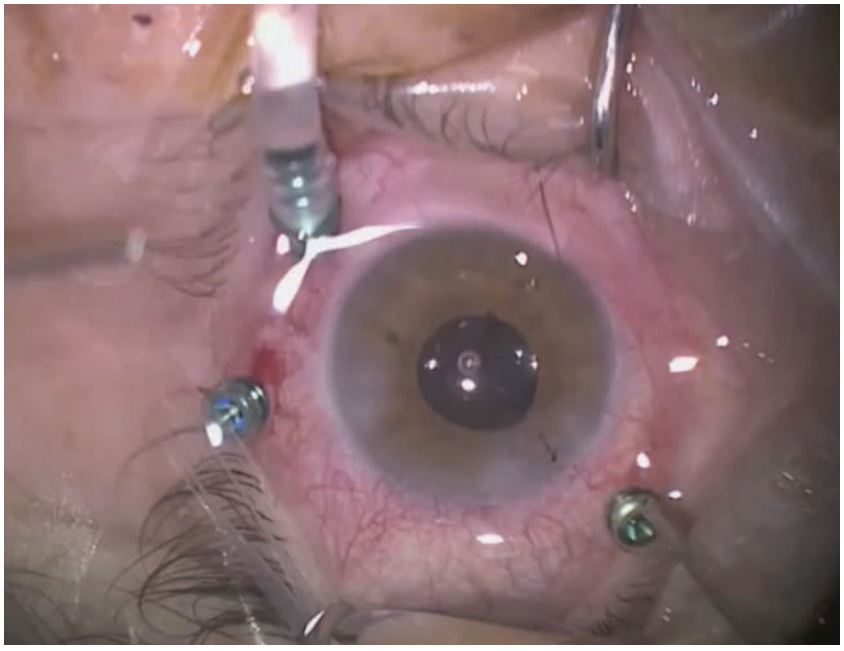

Figure 3. After inserting the intraocular lens into the bag and removing the viscoelastic, the wound is hydrated. Most tunneled corneal incisions less than 2.8 mm wide will seal well with hydration alone, but if wound stability is in doubt a single 10-0 nylon suture can be used for the main incision.

specialists. The following scenarios may provide ideas about how to approach these concerns.

Preoperatively, the retina surgeon must do the IOL power calculation. In our practice's experience, biometry with the IOLMaster (Carl Zeiss Meditec) has given consistent results. The only time we don't insert an IOL is if the patient has a macula-off retinal detachment, as the calculations may be inaccurate. In such cases, we perform phacoemulsification without IOL implantation.

After the retina is attached, we send the patient to the referring anterior segment colleague for secondary IOL implantation in the bag. If the patient was not referred, we implant the IOL in a secondary procedure after performing the IOL measurements and calculations.

Preoperatively, we check for the presence of small pupils or posterior synechiae so that we can be ready to use iris hooks if necessary during surgery. We assess the red reflex, especially in vitreous hemorrhages, and use trypan blue dye if the reflex is poor. Use of trypan blue or iris hooks allows for coding at a higher level.

Our office informs the patient that, due to the retinal pathology, multifocal IOLs are probably not indicated. A monofocal accommodating IOL may be a better choice if the patient desires intermediate and near vision independent of spectacles.

How Phaco and Vit Differ

Intraoperatively, most of the basic surgical steps for phacoemulsification and vitrectomy procedures are similar, with the following exceptions.

We insert all three ports before starting phacoemulsification (*Fig-*

ure 1, page 21). We do this because inserting the ports after phacoemulsification creates a slightly higher risk of the main cataract incision gaping due to the pressure applied for port insertion.

We make sure to insert the superior ports closer to the horizontal meridian so that they don't get in the way of the phaco handpiece and chopper. When operating on a right eye and sitting at the patient's head, we insert the infusion port inferotemporally.

After we visualize that the infusion port is in the proper position, we turn on the infusion, then place the two superior ports in the usual manner transconjunctivally at the 2:30- and 9:30 clock positions (*Figure 2*). We prefer to use valved trocar systems; however, one can use plugs when valved trocar systems are not available.

We then turn off the infusion so that it can be connected to the phaco handpiece, and start the phacoemulsification portion of the procedure with the side port incision at 2 o'clock and the main incision at the 10-o'clock position.

We have a low threshold for using trypan blue dye if there is a doubt regarding the red reflex, especially with vitreous hemorrhages. If we anticipate the need to use gas at the end of the vitrectomy, we make the capsulorhexis slightly smaller than usual to prevent anterior subluxation of the IOL in the postoperative period. This is a rare occurrence. In the few postoperative IOL subluxations we've encountered, we've managed to put them back in position at the slit lamp with a 30-gauge needle.

For very dense cataracts, we use ample dispersive viscoelastic material to coat the endothelium prior to phacoemulsification.

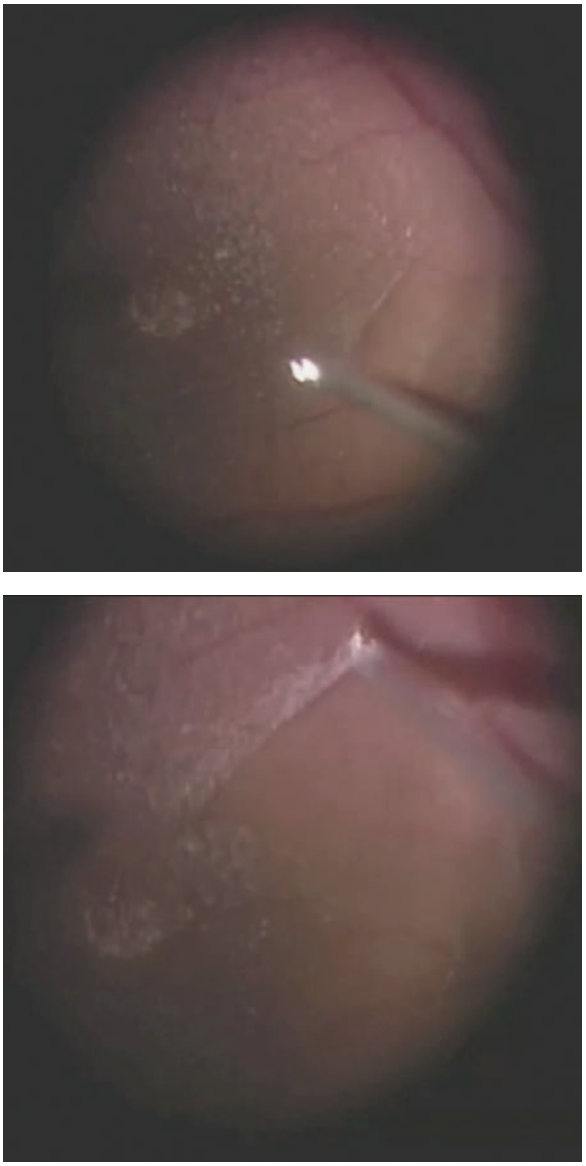

Figure 4. After initiating the membrane peel with ILM (internal limiting membrane) forceps, we use an ILM splitter to lift the membrane (top). Kenalog particles suggest the presence of an epitretinal membrane, and the peeling commences (bottom).

After we insert the IOL into the bag and remove the viscoelastic, we hydrate the wounds (there is no need for sutures). Most tunneled corneal incisions less than 2.8 mm wide will seal well with hydration alone. If wound stability is in doubt, we use a single 10-0 nylon suture for the main incision (*Figure 3*), then start the vitrectomy in a standard approach after turning on the infusion (*Figure 4*).

Conclusion

Many of us foresee a time when third-party payers will prefer retina surgeons who can manage both cataract and retina issues due to the potential for increased benefits to patients and efficiencies for the health-care system. For these reasons, it behooves the young retina fellowship trainee to avoid losing the phacoemulsification skills learned during residency. Additionally, vitreoretinal fellowship training programs should encourage more phacovitrectomy procedures, given the multitude of benefits outlined here.

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Focus on Surgery

A NOVEL APPROACH FOR RD IN VIRAL RETINITIS

The PFO-foscarnet pocket is an option for treating a detached retina in this difficult clinical setting.

David R.P. Almeida, MD, MBA, PhD, and Eric K. Chin, MD

First described as acute retinal necrosis by Akira Urayama, MD, and colleagues at Tohoku University in Japan in 1971,[1] viral retinitis typically manifests as a progressive occlusive necrotizing vasculitis involving retinal and choroidal vasculature with subsequent retinal detachment.[2,3] Bilateral viral retinitis, also known as bilateral ARN (BARN), occurs in up to a third of cases.[3,4]

Viral retinitis is rare—0.63 cases per 1 million population per year—with equal incidence among males and females and a large variation in age of presentation.[5,6] However, mixed-mechanism retinal detachment secondary to viral retinitis is common, occurring in 20 to 75 percent of these eyes, with resultant poor visual outcomes.[7-10] These complex RDs require surgery. Here, we discuss our own study of surgical and anatomic outcomes in patients with RD secondary to viral retinitis[11] and highlight a novel surgical technique called the "PFO-foscarnet pocket."[12]

Etiology of Viral Retinitis

Diagnosis of viral retinitis is based on the American Uveitis Society clinical criteria that include:

- Focal, well-demarcated areas of retinal necrosis in the peripheral retina.
- Rapid and circumferential progression of necrosis.
- Evidence of occlusive vasculopathy.
- Prominent inflammatory reaction in the vitreous and anterior chamber.[13]

Etiology in immunocompetent patients is varicella zoster virus in 50 percent, herpes simplex virus in 25 percent, Epstein-Barr virus in 15 percent and cytomegalovirus (CMV) in 1 percent, although the latter is much more common in immunocompromised patients.[14–16]

Polymerase chain reaction analysis of aqueous and vitreous samples is the gold standard for diagnosis, with a sensitivity of 95 percent and specificity of 97 percent,[17-19] and for monitoring disease course and response to therapy via viral load quantification.[20-22] Treatment standards currently call for oral medications such as acyclovir (800 mg five times per day),[23] valacyclovir (1 g t.i.d.)[24] or famciclovir (500 mg t.i.d.).[25] They seem to have similar efficacy to the traditional

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DISCLOSURES: Dr. Almeida is cofounder of Citrus Therapeutic and disclosed relationships with Allergan and Genentech. Dr. Chin has a relationship with Citrus Therapeutics.

intravenous acyclovir (1,500 mg/m_2 body surface area) regimen.[26]

Oral agents like valacyclovir and famciclovir have superior bioavailability and central nervous system penetration compared to acyclovir and seem to have utility in both the initial treatment and maintenance therapy of patients with viral retinitis.[3] A six-to-eight-week induction period followed by a three-to-six-month maintenance phase seems to be effective in this often chronic and recurrent clinical course.

RDs in Viral Retinitis

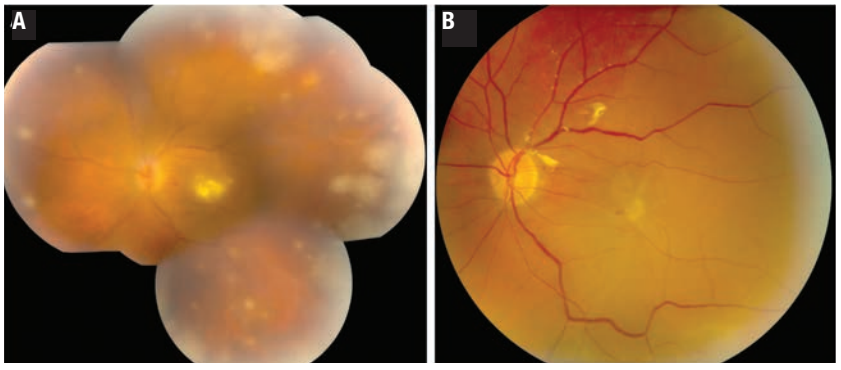
RDs in viral retinitis usually occur after the acute phase of infection and are secondary to vitreous traction on the necrotic retina and inflammatory membranes, resulting in stretch holes and a partially rhegmatogenous component.[27]

In our study, all cases underwent three-port pars plana vitrectomy (PPV) with induction of a posterior vitreous detachment, if not already present. We employed membrane peeling, retinotomies and retinectomies to remove inflammatory vitreal and retinal membranes as well as necrotic retina (*video available at bit.ly/2eKmGzW*), and performed tamponade with 1,000-centistoke silicone oil in 11 of 12 eyes. During PPV, we placed a scleral buckle in 10 eyes (83.3 percent).

Initial surgery achieved successful anatomic re-attachment of the retina in all cases, and no re-detachments occurred during the follow-up period. In 50 percent of eyes, we successfully removed silicone oil at a later date with no recurrence of retinal detachment during the study period.

Foscarnet During Surgery

Although oral valacyclovir penetrates intraocular tissue, we know that direct intravitreal antiviral therapy may be more effective. Delivering intravitreal therapies in the setting of silicone oil tamponade is challenging. One must use caution because delayed clearance of intravitreal antivirals from silicone oil-filled eyes may result in retinal toxicity.



Preoperative montage color fundus photography illustrates retinal whitening in the macula with peripheral retinal necrosis (A) in a patient with optic nerve involvement with mild disc hyperemia, edema and moderate vitritis with a macula-off rhegmatogenous retinal detachment. Presenting visual acuity was 20/800. Postoperative color fundus photography (B) shows results two months after cataract extraction with placement of a posterior chamber intraocular lens combined with 23-gauge pars plana vitrectomy and silicone oil tamponade. Final visual acuity was counting fingers.

Unlike acyclovir or gancyclovir, antiviral foscarnet does not require thymidine kinase activation, so resistance is uncommon. Foscarnet selectively inhibits viral polymerase and can rapidly inactivate the virus with a short contact exposure time. Consequently, we have successfully incorporated this therapy at the time of surgical repair.[12] The steps in the technique are:

- ***Multiplane chromovitrectomy.*** This step facilitates retinal detachment repair with concurrent intraoperative intravitreal antiviral therapy prior to silicone oil tamponade.
- ***After removal of all vitreous and necrotic retina, injection of perfluoro-n-octane (PFO) liquid over the posterior pole.*** This flattens any posteriorly detached retina up to the most posterior edge of any breaks, creating a PFO-infusion fluid meniscus. At this point, there are two distinct phases in the vitreous cavity: a PFO bubble over the posterior pole; and a layer of balanced salt solution (BSS) more anteriorly. The PFO flattens and immobilizes the retina more posteriorly in its usual manner.
- ***Injection of approximately 0.1 to 0.2 mL of foscarnet (2.4 mg per 0.1 mL) over the PFO into the BSS more anteriorly.*** This creates a PFO-foscarnet "pocket" or "shell" that allows the foscarnet to penetrate the retina while the PFO stabilizes

Take-home Point

Varicella zoster virus is the most frequent cause of viral retinitis, and oral valacyclovir has been a safe and effective treatment. In patients with secondary retinal detachment, vitrectomy with silicone oil tamponade and sometimes scleral buckle placement yield excellent anatomical results. Our novel PFO-foscarnet pocket can allow for intraoperative antiviral coverage in these patients, who often require long-acting silicone oil tamponade.

the posterior retina.

• ***At this point, laser retinopexy or any additional vitrectomy or retinectomy can be performed.*** If needed, this will allow the intravitreal foscarnet to have increased exposure time to the diseased peripheral retina.

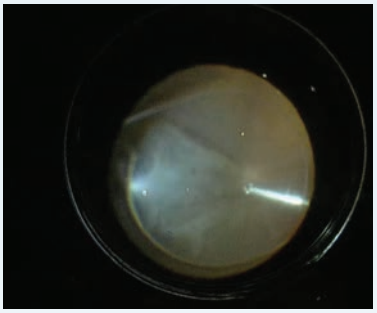
• ***Air-fluid exchange.*** Upon completion of the vitrectomy, a soft-tipped extrusion cannula helps to perform an air-fluid exchange by first removing the anterior BSS-foscarnet followed by the more posterior PFO.

• ***Foscarnet wash.*** In the final step, injection of three to five drops of foscarnet over the posterior pole in the air-filled eye performs a foscarnet wash. This allows the foscarnet to penetrate any posterior retina previously inaccessible owing to the PFO placement. The silicone-tip extrusion needle helps to remove the foscarnet and any remaining BSS. The technique allows stabilization of the detached retina while allowing for antiviral washout during vitrectomy.

We identified optic nerve involvement as a poor prognostic factor because only eyes without optic nerve involvement were able to achieve visual acuity of 20/100 or better. We used the proposed absolute criteria for optic nerve involvement in ARN to determine optic nerve involvement according to three criteria:

- Afferent papillary defect not consistent with the retinal findings.
- Poor correlation between retinal findings and visual acuity.
- Sudden deterioration of visual acuity to 20/100 or worse without corresponding retinal changes within a 24- to 36-hour interval.[28]

Visual acuity seems unlikely to improve in these cases. Subsequent interventions primarily aim to prevent involvement of the fellow eye, chronic retinal detachment and phthisis bulbi.



View the Video
A video that demonstrates the technique Drs. Almeida and Chin discuss is available at bit.ly/2eKmGzW.

Our novel PFO-foscarnet pocket allows for intraoperative antiviral coverage in this challenging group of patients, who often require long-acting silicone oil tamponade.

How We Conducted Our Study

Our study of surgical outcomes of retinal detachment secondary to viral retinitis was a retrospective, consecutive case series of patients with rhegmatogenous RD (RRD) secondary to viral retinitis between 2006 and 2013. Inclusion in the study required confirmed vitreous or aqueous culture results. Outcome measures included effect of antiviral therapeutics, time to retinal detachment, course of visual acuity, as well as anatomic and surgical outcomes.

The study identified 1,259 consecutive patients with RDs; 12 eyes in 10 patients had an RRD secondary to viral retinitis (prevalence: 0.95 percent). We followed patients for an average of 4.4 years.

Polymerase chain reaction analysis identified varicella zoster virus, herpes simplex virus and cytomegalovirus in six, two and two patients, respectively. Median visual acuity at presentation was 20/100 and median final VA was 20/1250 with a statistically significant deterioration in vision. The median time to retinal detachment from initial presentation with active viral retinitis was 4.5 weeks and average time of eight weeks. Fifty percent of cases had macula-involving RDs.

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Focus on Surgery

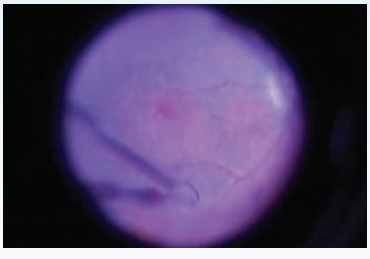
A SIMPLIFIED, 3-STEP APPROACH TO MACULAR PEELING

Biologic stain facilitates this 'real-world' approach for persistent or recurrent ERMs.

By Robert A. Sisk, MD

Vitreomacular interface disorders commonly cause blurred vision and distortion in patients over age 40.[1,2] A variety of secondary causes, including a torn or detached retina, uveitis and retinal vascular diseases, can create vitreomacular traction or epiretinal membrane formation, but most cases are idiopathic.[3,4] The decision to treat these disorders depends upon multiple factors, including the degree of both objective and subjective visual impairment, risk of worsening vision without treatment, fellow eye status, lens status and the risk of surgical complications.

There are no guidelines from the American Academy of Ophthalmology or Medicare regarding the indications for macular surgery for vitreomacular interface disorders, so the decision for treatment ultimately rests with the surgeon's best judgment and experience.[5]



View the Video
A video that illustrates Dr. Sisk's peeling technique is available at bit.ly/2eC27Za.

There are many variations in membrane peeling techniques, including the use and choice of biologic stains, peeling of the internal limiting membrane (ILM) and the tools or techniques used to accomplish these maneuvers. Controversies over these are beyond the scope of this article and reflect surgeon preference more than science.

With that in mind, I humbly present my preferred technique for macular surgery—not as science or dogma, but as real-world knowledge accumulated from successes and failures, intended to help you avoid "teachable moments." Regardless of preferences, an agreeable goal for macular surgery is to relieve symptomatic macular distortion without iatrogenic damage to the macula.

Surgical Approach and Prep

Macular surgery can be intimidating to new vitreoretinal surgeons given the fragility of the retina to manipulation and the importance of the macula to functional and occupational vision. The vitreous, retina and often the abnormal epiretinal tissue are optically clear, which adds significant challenge to initiating membrane peeling and determining an endpoint.

Here, I present a simple tech-

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nique that is effective for removal of most epiretinal membranes. It utilizes the advantages of a biologic stain, "heavy" indocyanine green (ICG) diluted in 5% dextrose solution, to differentiate normal from abnormal structures.[6-9] My preferred technique is to peel the ILM in all cases, lifting the epiretinal membrane (ERM) with the underlying ILM scaffold and removing the substrate for persistent or recurrent epiretinal membranes. Complete ILM peeling of the macula is not safe in all cases, and is not mandatory for visual gains.[10]

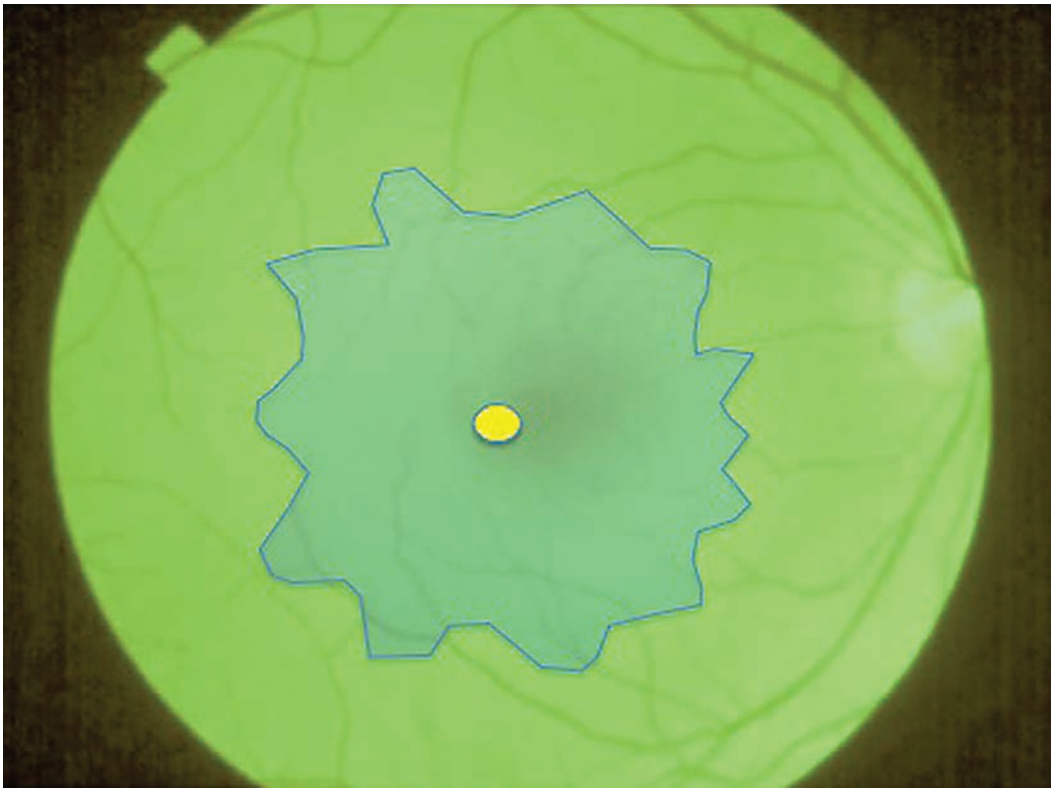

Figure 1. With infusion pressure lowered, apply "heavy" indocyanine green stain to cover the entire macula. Allow it to settle for 10 seconds then remove, leaving a robust green staining of the internal limiting membrane and negative staining of the epiretinal membrane complex.

Critical steps for planning surgery include evaluating the status of the posterior hyaloid face and the configuration of the tractional complex with funduscopy and spectral domain optical coherence tomography.[11-14] Although most idiopathic ERMs occur after a posterior vitreous detachment (PVD), vitreoschisis (splitting of the posterior hyaloid face into layers) with a retained layer of posterior cortical vitreous covering the retina commonly accompanies secondary causes of vitreomacular interface disorders, particularly vascular and inflammatory diseases, or with chronic macular hole.[15-19]

Applying Biologic Stains

After core vitrectomy, elevation of the posterior hyaloid face is required to apply biologic stains to the ERM or ILM and to gain access with instruments for membrane peeling. SD-OCT can identify areas of vitreous attachment, vitreous traction and surgical planes between the epiretinal tissue and the inner retina. Aspiration with the vitreous cutter just over the optic disc with or without diluted triamcinolone acetonide stain can induce a PVD.

SD-OCT can also provide information about the character and anticipated surgical behavior of the ERM. For a diffuse, sheet-like ERM with uniform thickness that extends beyond the boundary of a standard 6-mm horizontal raster scan, the membrane is often elastic, cohesive and stains poorly with both triamcinolone and "heavy" ICG. This

Take-home Point

In the absence of guidelines for macular surgery for vitreomacular interface disorders, the surgeon must rely on his or her best judgment and experience for treatment. This article describes a technique for membrane peeling that uses indocyanine green biologic stain and peeling of the internal limiting membrane and epiretinal membrane complex together.

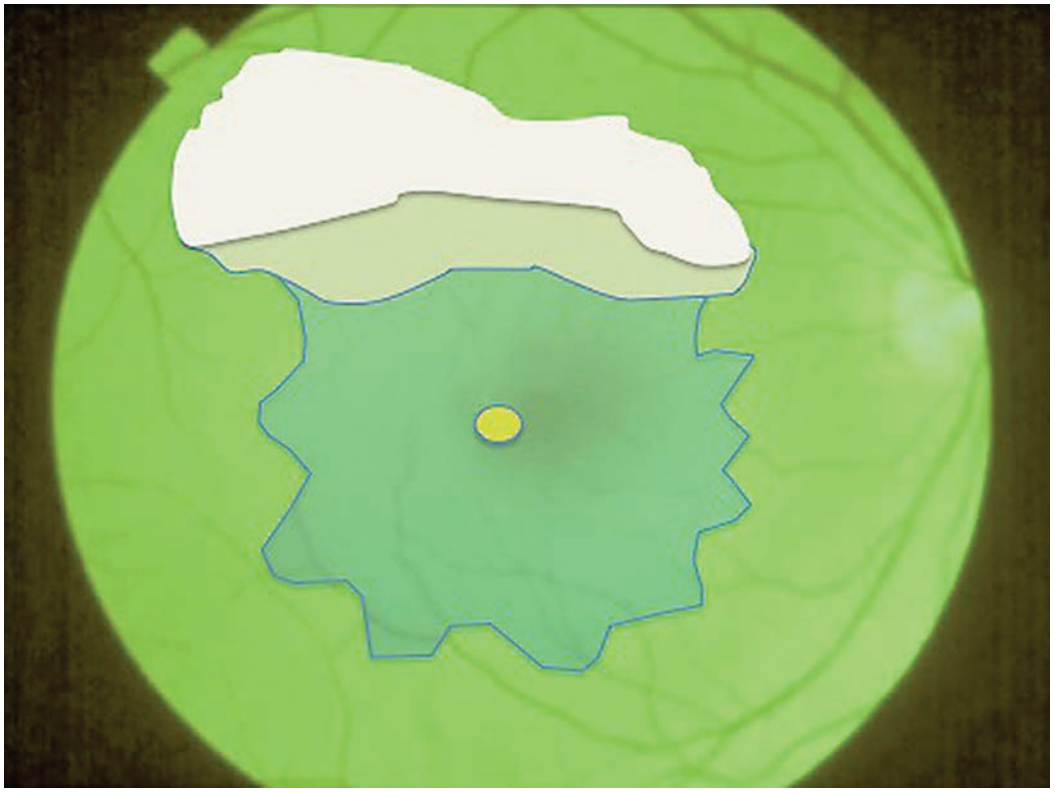

Figure 2. To initiate peeling of the internal limiting membrane, create a horizontal contiguous row of breaks in the ILM with a scraper, and use ILM forceps to advance the edge of elevated ILM to the border of the epiretinal membrane.

type of ERM commonly appears in patients with a history of diabetic retinopathy or posterior staphyloma from pathologic myopia.

In eyes with a history of uveitis, the ERM and ILM are often friable. Attempted ILM peeling may require multiple regrasps and can induce iatrogenic macular trauma. Cases with vitreomacular traction or macular hole on OCT typically have strong adhesions at the foveal Müller cell cone. You must use caution when peeling across the fovea in such cases, as iatrogenic traction could induce or enlarge a full-thickness macular hole.

Preoperative disruption or disorganization of retinal lamination at the fovea by OCT is an important prognostic indicator for limited visual improvement despite relief of vitreomacular interface disease.[13]

The Surgical Technique

• ***Step 1: Apply 'Heavy' ICG Stain.*** After performing core vitrectomy and confirming the elevation of the posterior hyaloid face, apply approximately 0.3 mL of "heavy" ICG for 10 seconds over the macula without a fluid-air exchange (*Figure 1*). The volume injected should be sufficient to cover the macula as a confluent puddle.

Three techniques can facilitate stasis of the ICG stain over the macula: using valved cannulas; reducing infusion pressure; or suspending the automatic intraocular pressure-regulating feature on the vitrectomy system. Avoid longer durations of ICG exposure to reduce the risk of ICG toxicity.[20-25] Prolonged exposure also increases fragility of the ILM, resulting in shearing of a brittle substrate into small fragments rather than the desired native elasticity that facilitates cohesion during peeling.

Once the ICG is removed, the ILM should stain moderately to intensely green; negative staining will reveal the ERM. If the ERM is diffuse or the plane between the membranes and inner retina is minimal on SD-OCT, ICG staining of the underlying ILM may be more patchy. An absence of initial staining indicates a diffuse ERM that will require a pinch peeling technique; it is unlikely to cleave cleanly with a scraper.

• ***Step 2: Initiate ILM Peeling.*** Using a scraper or forceps, fracture the ILM at a natural weak point overlying the large retinal vessels, at the inferior arcade. Angle conformal ILM forceps most tangentially when reaching across the horizontal and vertical midlines from their respective sclerotomy. This helps to prevent an asymmetric, deep grab that could result in bleeding or trauma to the inner retina.

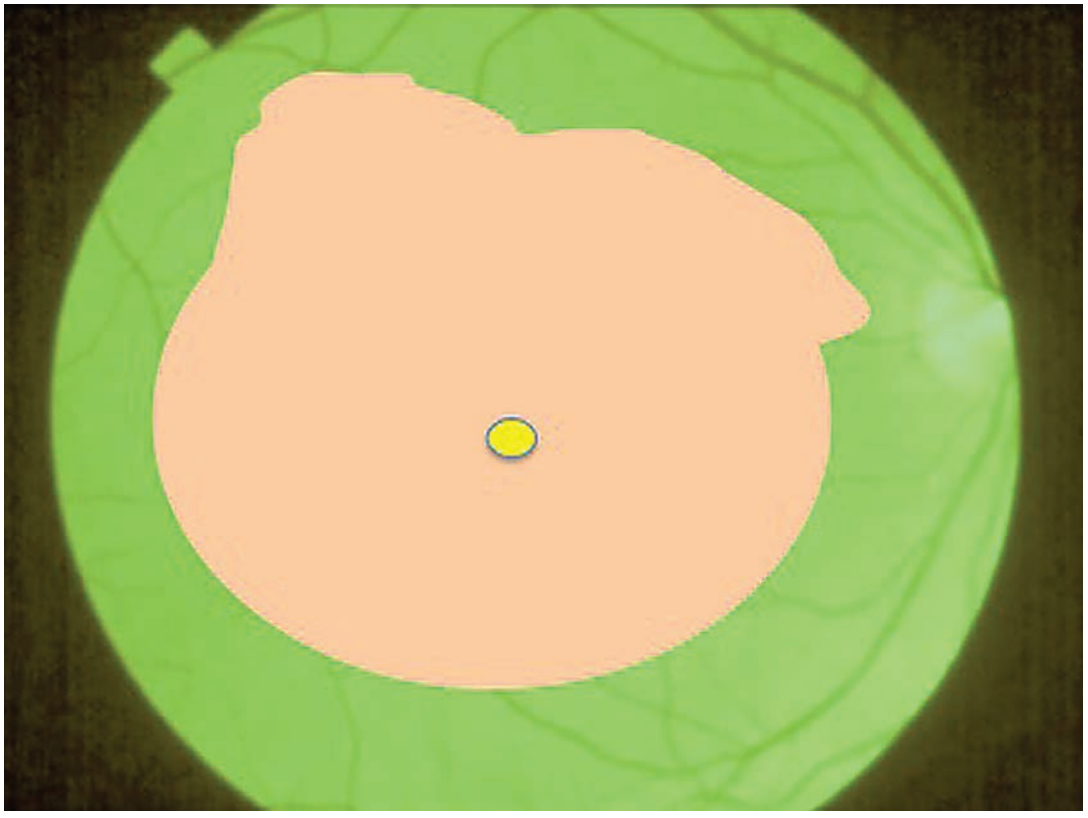

Figure 3. Peel the internal limiting membrane and epiretinal membrane complex together, removing the complex with forceps as a single sheet to release all traction from the macula.

However, if no staining appears inferiorly, you can use the temporal quadrant. Beginning the peel from the superior or nasal quadrants can be problematic because of added risks: the instrument blocks the view of what will be peeled; scrapers are more likely to create trauma when oriented more vertically than tangentially; and the papillomacular bundle should never be touched.

My preferred technique is to scratch toward my instrument's sclerotomy with a diamond-dusted membrane scraper or nitinol loop to create a series of contiguous horizontal edges of elevated ILM for a broad plane to continue the peel. This allows multiple opportunities for regrasping with ILM forceps if the ILM shears at any point.

Initiating the ILM peel distant to the fovea affords room for regrasping without risk of traumatizing the fovea, if the ILM shears posteriorly. Peel the ILM to the boundary of the ERM, trying to keep as broad an edge as possible. Keep the forceps close to the retinal surface when propagating the peel to prevent narrowing of the elevated band by shearing. Remember, the macula is a concave structure, except where there is traction or edema. Try not to amputate the peeled flap of stained ILM in order to preserve landmarks for regrasping.

• ***Step 3: Peel the ILM and ERM Complex Together***. Once the ILM peel reaches the boundary of the ERM, release and fold the peeled ILM edge over to expose the base of the ERM to grasp the ERM and ILM together (*Figure 2, page 29*).

Pearls for Membrane Peeling

1. Formula for "heavy" indocyanine green: Inject 0.5 mL diluent into the ICG bottle and shake until powder enters solution. Then add 24.5 mL of 5% dextrose (D5W) solution. Mix thoroughly. Draw into 1-cc syringe with a 25-gauge, 5/8-inch needle for injection. Alternatively, add 25 mL D5W to ICG bottle and mix thoroughly.

2. Inexpensive stain: One vial of ICG costs about $99 and can be used for multiple cases in a given day, which is cost-effective in many surgery centers.

3. Maximize efficiency: I prefer 23-gauge instruments for faster core vitrectomy and the broader platform for greater purchase made possible by 23-gauge internal limiting membrane forceps. Most cases take between 10 and 15 minutes, depending on how cohesive the membrane is during peeling.

In eyes with diffuse macular ICG staining, which occurs with thin membranes and those with a prominent cleavage plane on SD-OCT, you may continue the peel through the fovea without specifically regrasping to include the ERM.

Closing the forceps to sweep and then pin the edge is an effective technique to control the floating peeled tissue that otherwise is subject to movement from the fluidics of the infusion. I prefer to reduce infusion pressure and turn off the automated intraocular pressure control feature during membrane peeling to reduce this movement. A higher infusion pressure may be preferred in eyes with a risk for bleeding from retinal neovascularization as part of the ERM complex.

I prefer to peel through the fovea and nasal macula first to release traction from areas most likely to be producing the patient's visual complaints and to avoid regrasps that could traumatize these areas later in the peeling. If there is strong adhesion at the fovea, I peel circumferentially around the fovea before removing a plume of epifoveal tissue.

Again, try to sweep slowly with the forceps shallowly over the retinal surface to radiate and broaden the peel rather than shear or narrow it. If the vertically oriented strip amputates, it will leave two planes for circumferential peeling.

It's important to reorient the forceps perpendicular to the new edge and grasp as peripherally as possible to make the peel broad and avoid regrasps that would threaten the fovea. This technique closely resembles propagation of an anterior capsulorhexis and has been coined a "maculorhexis." If all stained landmarks have been lost, restaining with ICG may reveal new edges.

If the peeling requires multiple grasps, the ERM and ILM may cleave into separate planes. Restaining can reveal ILM remnants if you desire complete ILM peeling in the rhexis. Limit exposure times with ICG to avoid toxicity.

Most importantly, the goals of macular surgery should be at the forefront during peeling: 1) relieve traction from the fovea; and 2) avoid traumatizing the macula. Therefore, the surgeon should aim for good, not perfect, and avoid picking excessively at peripheral ERM or ILM remnants after accomplishing the primary goal of surgery.

Conclusion

Biologic stains enhance the visibility of normal and pathologic structures during macular surgery. This may improve safety by limiting manipulation of normal tissue, which is critical because the retina is inherently fragile.

The simple technique I've outlined here is effective for removing most ERMs and can be applied with any gauge surgery and with any vitrectomy system. We have not experienced safety issues with "heavy" ICG at our institution, and it has been cost-effective for our surgery center. RS

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NEW THINKING ON DIABETES AND THE RETINA

The process of retinal neurodegeneration precedes microvascular disease.

By Aaron M. Ricca, MD, Elliott H. Sohn, MD, and Michael D. Abràmoff, MD, PhD

It is well known that diabetic retinopathy presents clinically as microvascular changes and damage to the retina evident on ophthalmoscopy. But diabetes also causes damage beyond this classical presentation—quantifiable neuronal degeneration and neuroretinal thinning, specifically known as retinal diabetic neuropathy.[1-3]

Recent reports have suggested that retinal diabetic neuropathy (RDN) is an independent process, developing and progressing irrespective of the presence or severity of diabetic microvasculopathy. RDN manifests on optical coherence tomography as significant thinning of the retinal nerve fiber layer (NFL) and ganglion cell and inner plexiform layers (GCL+IPL).[3]

Many authors, including ourselves, have shown that this degeneration occurs in people with diabetes regardless of clinical markers of metabolic control. Progressive thinning can eventually lead to visually significant changes, such as loss of contrast sensitivity, dark adaptation and peripheral field loss.[2] Recognizing these changes is important for patient management and can lead to better understanding of the disease process, as well as novel therapies.

Diabetic Retinopathy Burden

In 2014, at least 422 million people were estimated to have diabetes mellitus worldwide, which is almost as many individuals affected during the "Spanish" influenza pandemic of 1918.[4]

According to the American Diabetes Association, the total economic burden of diabetes in 2012 was estimated at $245 billion.[5] Further estimates speculate that the total cost of diabetes attributable to diabetic retinopathy ranges anywhere from 10 percent to upwards of 42 percent.[6]

Beyond the massive economic impact, DR accounts for a significant component of diabetes-related morbidity. It is the leading cause of vision loss in people with diabetes, and it is one of the chief causes of irreversible blindness in working-age adults across the world.[7]

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Microvascular Damage Not the Whole Story

Traditional thinking has held that diabetes affects the eye through microvascular endothelial damage caused by advanced glycosylated end products. Histological analyses have shown that the earliest notable microvascular changes are pericyte loss followed by acellular capillaries.[8,9] This diabetic microvasculopathy manifests funduscopically with the well-known features of microaneurysms, venous beading, lipoprotein exudates and retinal edema.[10]

All of the sequelae of DR are attributed to microvascular harm, and taught as such to all ophthalmologists in training. The Basic and Clinical Science Course curriculum (BCSC), commonly thought of as a preeminent source for ophthalmic knowledge, lists diabetic retinopathy under the chapter title of "Retinal Vascular Disease."[11]

Also, HbA1c is well established as an accurate marker for diabetic control and microvascular damage. However, the Epidemiology of Diabetes Interventions and Complications/Diabetes Control and Complications Trial studies have shown that HbA1c explains only 11 percent of the variance in developing or worsening DR, indicating other factors are involved.[12] Recent evidence and investigation suggests that microvascular damage is not the complete story regarding diabetic ocular disease.

RDN as an Independent Entity

Histological analysis of postmortem human retinal tissue in people with diabetes identified retinal neurodegenerative changes such as loss of ganglion cell bodies, glial reactivity and neural apoptosis.[13] These changes are evident *in vivo* as thinning of the neuroretinal layers, which are measurable on OCT through image analysis.[14]

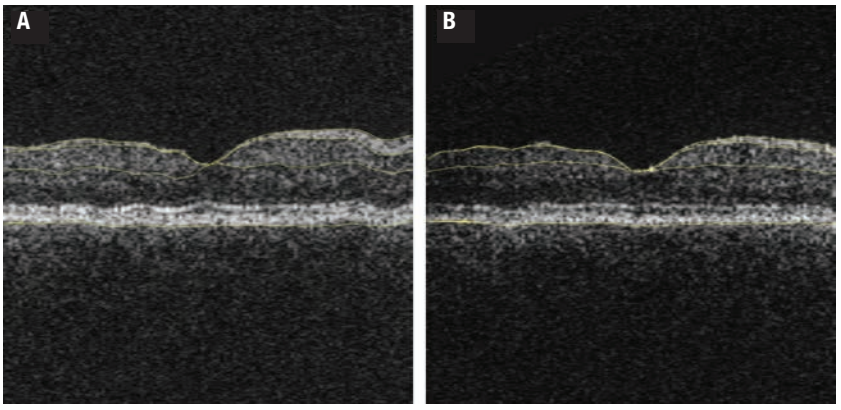

Figure 1. Optical coherence tomography with segmentation performed in a fashion similar to that used in the longitudinal study analysis[1] in a patient with diabetes at the outset of the longitudinal analysis (A) compared to the same patient at the final follow-up demonstrating the cumulative thinning over the study duration (B). Yellow automated segmentation outlines the internal limiting membrane, nerve fiber layer-ganglion cell layer boundary, inner plexiform-to-inner nuclear layer boundary and basement membrane.

Recently, we showed with our collaborators that the NFL, GCL and inner plexiform layer (IPL) were thinner in people with diabetes when compared to age-matched controls.[2] These subjects had no or minimal DR on funduscopic exam.

Other studies in patients with diabetes and animal models have confirmed these findings, and a commonality among them is that retinal neurodegeneration, quantified either structurally or functionally, occurs when the retina also manifests microvasculopathy from diabetes.[2,15-17] However, the precise temporal relationship between microvasculopathy and RDN was not known until we studied this more carefully. We published these results earlier this year.[1]

Investigation into the pathophysiology of RDN has shown mechanisms such as oxidative stress, extracellular glutamate accumulation and a relative loss of neuroprotective factors synthesized by the retina to be likely causal of degeneration, and possibly independent of vasculopathy.[18,19]

Some investigations failed to find an association between RDN and other traditional markers of diabetes severity, such as HbA1c.[2] Although HbA1c correlates highly with proliferative DR, it may not be associated with RDN.[20] Others have also suggested that neurodegeneration is secondary to diabetes, but not related to diabetic vasculopathy, based on systemic investigations. One

Take-home Point

Emerging reports have supported the idea that retinal diabetic neuropathy (RDN) is an independent ischemic process. This article explores the authors' own study that found inner retinal degeneration in eyes that had no funduscopically evident diabetic retinopathy, and explores data that RDN is not ischemic in origin, but is instead an antecedent process that may be a causal factor in diabetic retinopathy and microvasculopathy in the retina and elsewhere.

example is that some studies show that people with diabetes can develop brain atrophy over time without an increase in the number of infarctions.[21] RDN has also been shown to be directly related to peripheral neuropathy in severity.[22]

Clinical Significance of RDN

In glaucoma, progressive neuroretinal thinning is the likely mechanism of peripheral and eventual central vision loss. Thus, it is not unreasonable to think that RDN has a similar effect on vision. Our own reports have shown an association between the severity of RDN and vision loss on perimetry.[2,15] Others have also reported functional deficits of RDN via measurable abnormalities in electroretinography (ERG) and loss of contrast sensitivity and dark adaptation.[17]

Anthony Adams, OD, PhD, and colleagues recently studied ERGs in subjects with diabetes but no baseline DR and found that early ERG changes can predict if and where future DR, such as microaneurysms, will develop.[16] Investigations in both animal and human models have strongly supported the idea that RDN is a separate disease process from diabetic microvasculopathy, but none have established which came first.

The need to better determine whether RDN or diabetic microvasculopathy occurs first is clear, because this can have profound effects on how clinicians manage people with diabetes and what the focus of research on prevention of vision loss should be. The results could also impact the relationship of diabetes-related eye changes to other neural changes in the peripheral and central nervous systems.

Based on the classic World Health Organization (WHO) screening criteria applicable to all conditions, RDN would not currently qualify.[23] Currently, WHO recommendations for detecting or screening for diabetic retinopathy include various modalities such as photography and dilated fundus examination.[24] Although no known treatment or way to prevent RDN exists, expansion of these protocols to include evaluation of RDN may be warranted in the future.

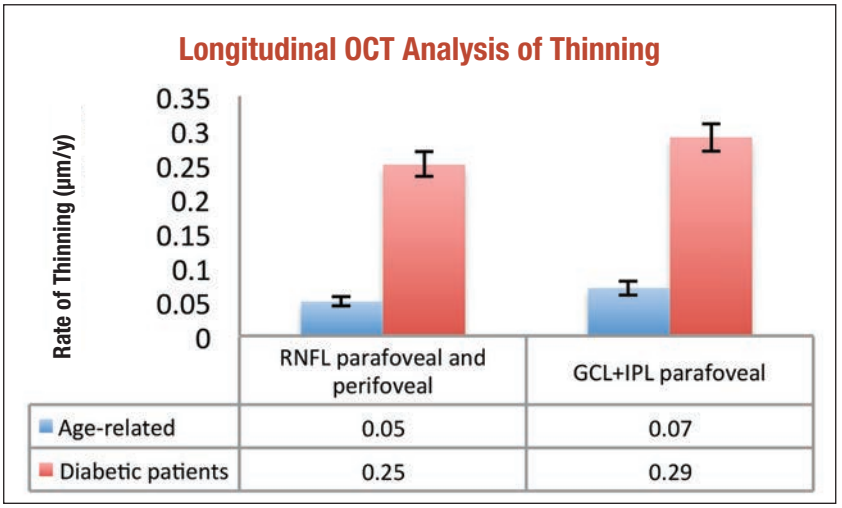

Figure 2. Progressive neuroretinal thinning (per year) in people with diabetes[1] far surpasses age-related thinning in people without diabetes.[25]

Human Studies of RDN

To better understand the relative timing of whether RDN or microvasculopathy occurs first, we evaluated retinal changes in humans with diabetes and in two different mouse models.[1] We studied human eyes via a prospective OCT analysis study as well as histological analysis of donor eyes of people with diabetes compared to controls. In both of these studies, the subjects with diabetes had no DR or minimal signs.

Our prospective study involved a cohort of 45 people with diabetes with no or minimal DR, following them with annual OCT analysis over an average of 73 months. Subjects had a mean HbA1c of 8.2 percent at baseline. We performed regular measurements of HbA1c, color fundus photography and OCT imaging. Subjects developed significant inner retinal thinning over the course of the study regardless of their DR status (*Figure 1, page 33*).

NFL thinning occurred at an average rate 0.25 µm/year; parafoveal GCL+IPL thinning occurred at a rate of 0.29 µm/year, after correction for age, sex, HbA1C status, DR status, blood pressure, DR progression and duration of diabetes. This thinning was statistically significant when compared to the normal age-related rate of thinning, and was readily apparent over the duration of the study (*Figure 2*).

Using the same methods, our collaborators previously established the normal rate of age-related thinning of the NFL and GCL at 0.05 µm/year and 0.07 µm/year respectively.[25] We found that neuroretinal thinning correlated with the duration of diabetes before inclusion, but we found no correlation between HbA1c level

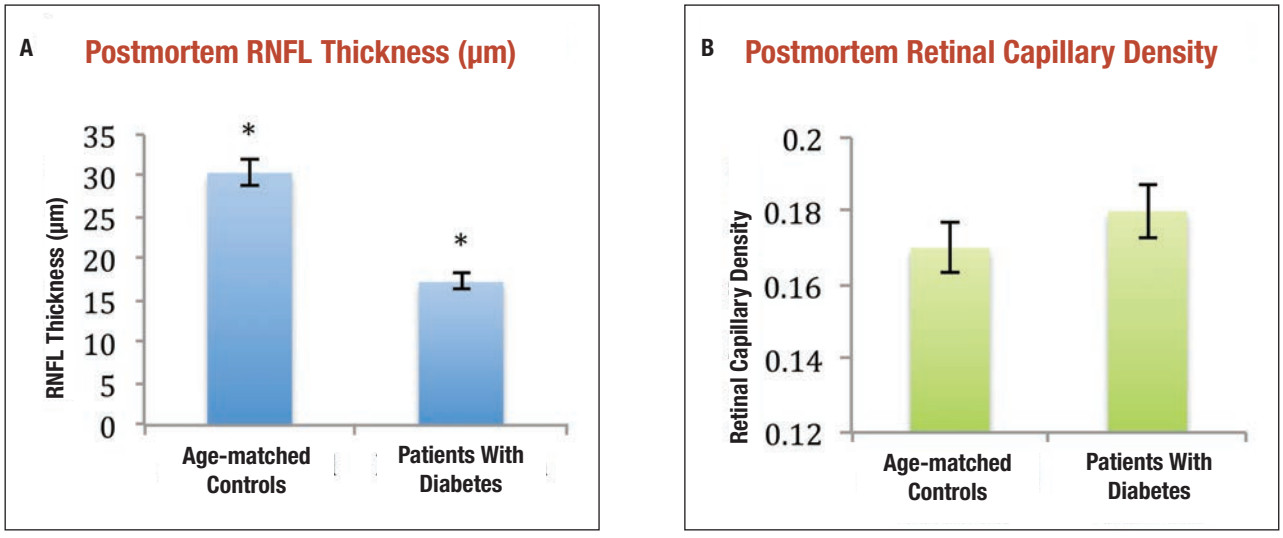

Figure 3. The average retinal nerve fiber layer thickness of cadaveric human eyes with diabetes but no or minimal diabetic retinopathy was significantly thinner than controls (A) (* indicates *p*-value <0.05), but retinal capillary densities were not significantly different between the same human donor subjects (B).[1]

and development of RDN.

In donor eyes of people with diabetes but no or minimal DR, we compared neuroretinal thickness to similarly aged controls without diabetes. The NFL was found to be significantly thinner in the DM eyes, 17.3 µm, compared to controls, 30.4 µm (p=0.03) (*Figure 3*).[1] We noted no statistically significant difference in retinal capillary density between the two groups, indicating a lack of microvascular damage. Thus, there is RDN in human donor eyes of people with diabetes that do not have clinical manifestation of DR or detectable microvascular changes on histological analysis.

Timing of RDN and Diabetic Microvasculopathy

In this same study, we evaluated RDN in two mouse models,[1] the findings of which corroborated the human data. A streptozotocin-induced mouse model of type 1 DM was used to show an average retinal thinning of 17.5 percent and 39.2

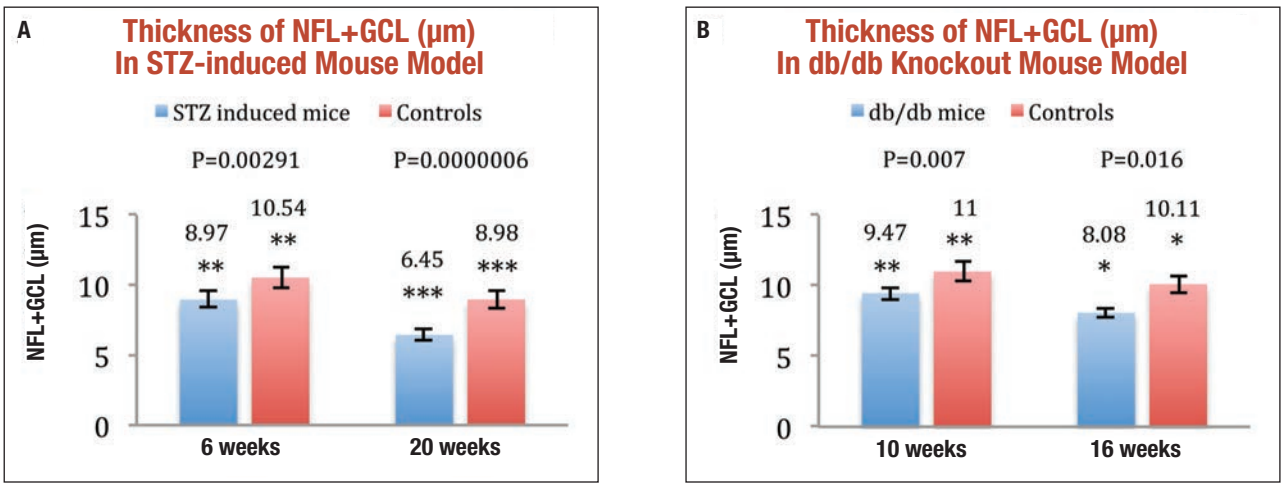

Figure 4. Streptozotocin-induced diabetic mice had significantly thinner nerve fiber layer and ganglion cell layer (NFL+GCL) than age-matched controls at both six weeks and 20 weeks after induction (A). Comparison of NFL+GCL thicknesses in db/db knockout mice (spontaneously diabetic) against age-matched controls at ages 10 and 16 weeks showed a less-significant difference (B).[1]

percent at six weeks and 20 weeks, respectively, using OCT analysis when compared to age-matched controls. Ganglion-cell density decreased as well, though there was no presence of diabetic microvasculopathy via histological analysis (loss of pericytes or acellular capillaries) at any time point in either group.[1]

Because some authors have suggested that streptozotocin itself could cause neural damage, we looked at a second model of mice that had spontaneous diabetes mellitus due to genetic mutation. In this db/db knockout mouse model that simulates type 2 diabetes, we compared retinal thickness against age-matched controls via OCT. The db/db mice were again found to have significantly thinner NFL+GCL by 13.9 percent and 20.1 percent at 10 weeks and 16 weeks of age, respectively (*Figure 4, page 35*).

These findings support the notion that RDN occurs before, and is independent of, diabetic microvasculopathy. For a more detailed description of our methods and results, please see the article we co-authored earlier this year in the *Proceedings of the National Academy of Sciences of the United States of America*.[1]

Future Trends in Management

If duration of diabetes could be found to correlate with clinically meaningful loss of function after a certain period of time, further studies could be useful in establishing monitoring guidelines and recommendations. Since ERG has been shown to predict development and location of DR, it could prove useful for early risk stratification and follow-up evaluation of people with diabetes with no baseline DR on exam.

Knowing who will develop microvasculopathy, and specifically when, is potentially useful for patient management. It may also be informative to compare perimetric analysis of patients with diabetes and those with glaucoma and similar amounts of NFL and GCL loss to determine if similar deviations exist. A study from our institution has shown a difference of 5 to 8 µm of the NFL and 1 to 8 µm of the GCL in patients with early vs. severe stages of glaucoma, and that these changes impart meaningful perimetric deficits.[26]

Quotable

The use of OCT and OCT angiography for early detection could provide an opportunity for a timely and economically feasible study to investigate preventative therapies early in the disease.

Based on data presented previously, diabetes patients could reach a level of retinal thinning near severe glaucoma over the course of 10 to 20 years. Because perimetry is used routinely to track glaucomatous progression, it may have a role in the assessment of DR, specifically long-standing RDN.

Currently we have no known agents to stop the development of RDN, though some candidates exist.[27] Now that we know that RDN precedes microvasculopathy, any neuroprotective agent that slows the progression of RDN may prove useful in concurrently slowing the development of microvasculopathy and severe vision-threatening DR if such a causal relationship exists.

The use of OCT and OCT angiography for early detection could provide an opportunity for a timely and economically feasible study to investigate preventative therapies early in the disease.

A Paradigm Shift

These findings present a significant evolution in our understanding of the pathophysiology of how diabetes affects the retina, and has implications for all diabetes-related complications. Much current literature supports systemic diabetic neuropathy as an independent ischemic process. Our published data supports the thought that RDN is not ischemic in origin, but is instead an antecedent process that has the potential to be a causal factor in DR and microvasculopathy in the retina and elsewhere.

As the study of diabetic neuropathy continues, retina specialists are afforded a unique opportunity for analysis, given our current modes of visualizing retinal disorders. As our knowledge develops, it may become important to use spectral domain OCT analysis to quantify RDN regardless of the presence of DR in people with diabetes. This knowledge could alter practice patterns and provide a turning point in the management and understanding of the disease. RS

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DECEMBER

8-10, 2016
10TH ASIA-PACIFIC VITREO-RETINA SOCIETY (APVRS) CONGRESS
BANGOK CONVENTION CENTER, CENTRALWORLD, BANGOK, THAILAND
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Registration: http://2016.apvrs.org/registration/

JANUARY 2017

14-16
AMERICAN UVEITIS SOCIETY 21ST ANNUAL WINTER SYMPOSIUM
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27-28
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3-4
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23-26
RETINA WORLD CONGRESS
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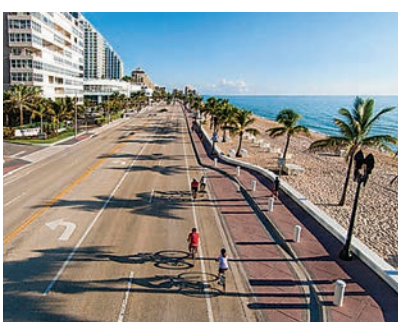

The beach promenade in Fort Lauderdale, Fla., host city of the Retina World Congress February 23-27, 2017.

MARCH

4-8
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24-25
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APRIL

1-2
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6-8, 2017
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MAY

6-11
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AUGUST

11-15
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'Soup & Sandwich' Silicone Oil Removal

Skimming technique avoids consequences of other approaches.

By Rachel Trussart, MD, FRCSC, Mark S. Mandelcorn, MD, FRCSC, Efrem D. Mandelcorn, MD, FRCSC, and Robert G. Devenyi, MD, MBA, FRCSC, FACS

Since its introduction in the 1960s, retina surgeons have broadly used silicone oil as an effective retinal tamponade in the repair of complex retinal detachment.[1] The surface tension of silicone oil confers its ability to act as an endotamponade by reopposing the neurosensory retina to the retinal pigment epithelium.

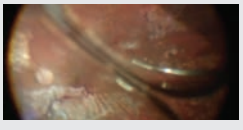
However, more recent reports have been published of significant visual deterioration following removal of silicone oil, and even of inexplicable and unanticipated sudden vision loss after uncomplicated silicone oil removal. Here, we describe the "soup-and-sandwich" technique we've used to remove silicone oil that may help avoid these vision-threatening complications.

Potential Consequences Of Silicone Oil

Over the past few decades, several studies have established the good intraocular safety profile of silicone oil in vitreoretinal surgery while rarely reporting toxic effects to the human retina.[2-5] Only a small number of papers have brought to light concerns over potential harmful consequences of silicone oil on animal retinal structures, particularly in longstanding use.[6-7] However, secondary anterior-segment complications to intraocular silicone oil, such as glaucoma, keratopathy and cataract, are well recognized.[8]

Since it can adversely affect nearly all ocular structures, silicone oil emulsification is a clinically serious complication. Moreover, in the emulsified state, silicone oil may not provide an optimal internal tamponade across the retinal surface. The duration of silicone oil in the eye, mainly after one year, seems to influence the propensity for emulsification.[9] For these reasons, expert retinal surgeons recommend removing the silicone oil when successful reattachment is accomplished and the retinal status appears to be clinically stable. The optimal timing remains controversial, usually ranging from three to 12 months.

The Pan American Collaborative Retina Study described significant visual deterioration following removal of silicone oil mostly secondary to retinal re-detachment, proliferative vitreoretinopathy and vitreous hemorrhage from proliferative diabetic retinopathy.[10] Other reports have emerged of inexplicable and unanticipated sudden vision loss after uncomplicated removal of silicone oil.[11-15] The published cases were originally fovea-sparing retinal detachment that remained attached during the entire surgery. These reports documented good visual acuity in these patients following initial vitrectomy and prior to oil extraction. None suffered from re-detachment, proliferative vitreoretinopathy, macular edema or epiretinal membrane.



View the Video

Drs. Trussart, Mark and Efrem Mandelcorn and Devenyi describe the 'soup and sandwich' technique for removal of silicone oil in this video available at: http://bit.ly/2dV02al

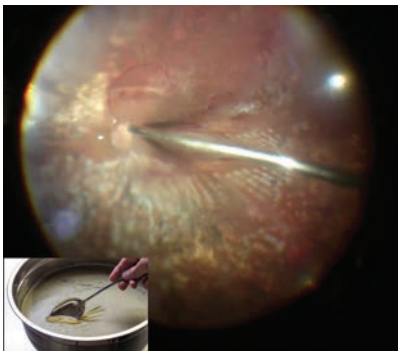


Figure 1. The relative density of silicone oil creates an incomparable air-liquid interface. The essence of our technique is to significantly improve silicone oil extraction by removing the thin layer of oil that is gathering on the interface, like skimming fat from soup broth (inset). Inset image: Brandon Matzek/Kitchen Konfidence

No other pathology could explain the vision loss. The incidence of this unexpected result ranges from 3 to 30 percent and appears to be linked to prolonged tamponade. The visual reduction seems to be severe and permanent. Different authors have suggested hypotheses to explain the underlying mechanism of the phenomenon, but the exact etiology of this sudden vision loss remains uncertain.[16-18]

This phenomenon has implications for vitreoretinal specialists and leads one to consider what needs to be done to avoid it. Surely, one must take special care to ensure a silicone oil evacuation that is as complete as possible, but this can sometimes be challenging. In fact, when infusing basic salt solution (BSS) in the vitre-

ous cavity, the silicone oil floats anteriorly and has a tendency to gather in the periphery, out of the range of the wide-angle viewing system.

Our silicone oil removal technique takes advantage of its physical properties. With the specific gravity of 0.97, silicone oil is lighter than BSS but heavier than air. This creates an incomparable air-liquid interface that allows the vitreoretinal surgeon to significantly improve silicone oil extraction by skimming away a thin layer of oil collecting on this interface, much like skimming the fat off of soup stock (*Figure 1*).

Surgical Technique

For our technique, we employ a standard three-port pars plana approach using a wide-angle viewing system. The silicone oil is aspirated actively using a 23-gauge automated viscous extraction device (Alcon Constellation) while infusing BSS (*Figure 2A*). The vitrectomy machine is set with a vacuum rate at 650 mmHg and with an intraocular pressure at 25 mmHg.

To improve the removal of silicone oil from the vitreous cavity, we preform an air-fluid exchange using a back-flush cannula. With the patient in the supine position, the air injected pushes back the silicone oil toward the posterior pole, sandwiching it between the air and the BSS (*Figure 2B*). This method is also handy in the presence of confined emulsified silicone oil droplets in the retro-iris plane.

To remove the oil overlay gathering on the interface, it is essential to place the tip of the back-flush cannula at the level of the air-fluid interface where a thin film of silicone oil can be observed.

Once the air-fluid exchange is taken down to the optic nerve, the vitreous cavity is partially infused with BSS. This essentially rinses the retinal surface of residual silicone oil that re-accumulates as BSS fluid refills the vitreous cavity. Be cautious during this step to re-infuse BSS at a low flow rate to avoid the stream of infusing BSS from creating an iatrogenic retinal break. The remaining air acts as a barrier by precluding the residual oil from traveling anteriorly again. In a similar manner, multiple sequential air-fluid exchanges are completed until all the oil has been skimmed off.

This silicone "soup-and-sandwich" skimming technique results in improved and more complete silicone oil removal.

Dr. Trussart is a vitreoretinal surgery fellow at the University of Toronto. Drs. Mark Mandelcorn, Ephrem Mandelcorn and Devenyi are attending vitreoretinal surgeons at the Toronto Western Hospital, Donald K. Johnson Eye Institute, University of Toronto.

DISCLOSURES: *The authors have no relevant disclosures.*

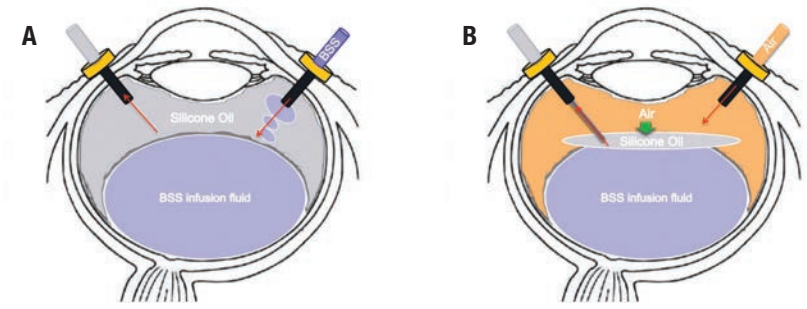


Figure 2. Employing a standard three-port pars plana approach, the silicone oil is aspirated actively using a 23-gauge automated viscous extraction device while infusing basic salt solution (BSS) (A). Then an air-fluid exchange using a back-flush cannula is performed (B). The air injected pushes back the silicone oil toward the posterior pole, *sandwiching* it between the air and the BSS. The tip of the back-flush cannula is maintained at the level of the air-fluid interface where the surgeon can see a thin film of silicone oil.

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

Handling Overfill for Single-Use Drugs

What CMS expects for documentation and reporting of leftover anti-VEGF drugs.

We continue to receive calls regarding the best way to document and code for non-compounded intravitreal anti-VEGF agents like Eylea (aflibercept, Regeneron) and Lucentis (ranibizumab, Genentech). The confusion involves documenting the disposal of the overfill, and whether reporting that disposal is required on a claim to Medicare.

Some of the injectable drugs that a retina practice uses contain a significant volume of overfill and creative offices occasionally inquire about using the overfill and/or billing it to a third-party payer.

CMS Sows Seeds of Confusion

In June 2016, the Center for Medicare and Medicaid Services (CMS) created confusion when it published Transmittal 3538 on the use of modifier JW, defined as "Drug amount discarded/not administered to any patient." The transmittal stipulates:

Effective January 1, 2017, when processing claims for Part B drugs and biologicals (except those provided under CAP), the use of the JW modifier to identify unused drugs or biologicals that are appropriately discarded is required.

The transmittal further requires providers to document any discarded drug in the chart, stating:

Also, effective January 1, 2017, providers are required to document the discarded drug or biological in the patient's medical record.[1]

Since the release of the transmittal, we are receiving questions like: "Do I have to report the discarded overfill on a claim?" and "Do I have to document the overfill in the chart?" Here, I'll provide some answers.

Role of JW Modifier

The transmittal failed to provide clarity regarding the reporting of discarded drug related to manufacture overfill vs. discarded drug included in the Food and Drug Administration-labeled volume/dosage. In August 2016, CMS released an FAQ discussing the JW Modifier and Transmittal 3538. This aimed to clarify the confusion the transmittal raised, stating, "The modifier is not required if no discarded drug is being billed to any payer." The FAQ further stated, "The JW modifier must not be used to report overfill wastage."[2]

CMS provides guidance regarding discarded drugs and biologicals. The Medicare Claims Processing Manual (MCPM) Chapter 17 §40, "Discarded Drugs and Biologicals," states:

When a physician, hospital or other provider or supplier must discard the remainder of a single-use vial or other single-use package after administering a dose/quantity of the drug or biological to a Medicare patient, the program provides payment for the amount of drug or biological discarded as well as the dose administered, up to the amount of the drug or biological as indicated on the vial or package label.[3]

As you can see, CMS provides reimbursement for wasted or discarded drugs. However, MCPM stipulates reimbursement for the discarded drug up to the amount on the package label. The amount of drug enumerated on the package label does not include manufacturer overfill. CMS reimburses drugs based on average sales price (ASP), determined by using the amount of product listed on the FDA-approved label. The final rule for the 2011 Medicare Physician Fee Schedule (MPFS) addressed the ASP calculation and intentional overfills in 42 Code of Federal Regulations (CFR) Chapter IV §414.904(a)(3):[4]

(i)CMS calculates an average sales price payment limit based on the amount of product included in a vial or other container as reflected on the FDA-approved label.

(ii) Additional product contained in the vial or other container does not represent a cost to providers and is not incorporated into the ASP payment limit.

(iii) No payment is made for amounts of product in excess of that reflected on the FDA-approved label.

The comments section of 42 CFR addresses the issue of overfill billing directly by stating:

In accordance with our current policy, as explained above, providers may not bill Medicare for overfill harvested from single-use containers, including overfill amounts pooled from more than one container, because that overfill does not represent a cost to the provider.[4]

Clearly, only the amount on the

FDA-approved package label is reimbursed as part of the ASP.

Documenting the Overfill

We receive further questions about what, if anything, should be documented regarding the disposal of the overfill. The same FAQ also discusses the required documentation for discarded drugs:

CMS expects that providers and suppliers will maintain accurate (medical and/or dispensing) records for all beneficiaries as well as accurate purchasing and inventory records for all drugs that were purchased and billed to Medicare.[2]

Single-dose vials, like Lucentis and Eylea used per the FDA label, do not contain any billable discarded drug. However, to avoid any probing questions from third-party payers, chart notes and operative reports should include notations regarding the discarded overfill.

Most physicians delivering intravitreal injections have detailed templates describing the procedure, including the dosage administered. We recommend adding a statement to the template or operative report about the discarded overfill, such as, "Manufacturer overfill was appropriately discarded."

There is significant confusion regarding the reporting and chart documentation of wasted and discarded drugs. When the waste represents manufacturer overfill, document the disposal in the chart/operative report, but do not add it to the claim using the JW modifier. RS

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By Richard Mark Kirkner »

Shaping Watson Computing for the Clinic

Cognitive imaging in ophthalmology could be about a year away. Here's what it might look like.

In about a year retina specialists may have a new clinical tool in the form of cognitive imaging that utilizes the computing power of IBM's legendary Watson. IBM has drawn 15 medical centers and medical device and technology companies into its Watson Health medical imaging collaborative, with Topcon Corp. and ifa Systems AG representing ophthalmology.

The headquarters of Watson Health in Cambridge, Mass.

First Up: Diabetic Retinopathy

Ophthalmologist P. Lloyd Hildebrand, MD, FACS, CEO of ifa subsidiary Inoveon and the point person in overseeing the development work in ophthalmology, says that imaging analytics for diabetic retinopathy is the first project the Watson Health development team is working on.

"That involves basically gathering representative images with all the biomarkers of the disease, teaching the machines to do algorithmic analyses, and then being able to integrate all those analyses to determine the severity of the disease," he says. Topcon acquired 50.1 percent of ifa Systems, a developer of health information technology for ophthalmology, last year.

During a presentation in the Technology Pavilion at the American Academy of Ophthalmology meeting last month in Chicago, Steve Tolle of IBM Watson Health said the idea is to bring information stored in tens of millions of patient records to the clinic. "What if I could present to you, as you treat a patient, data on thousands of patients with the same exact condition?" Tolle said. "Not from graphics, but based on the same exact lesion, the same exact disease. What would you do with that information?"

Watson's 'Voracious' Appetite

To ramp up, Watson is digesting massive amounts of data. "We've run 10 million images already through Watson, so Watson can now automatically detect what organ it's looking at and in some cases what condition the organ is in," Tolle said at the AAO.

"Voracious" is how Dr. Hildebrand describes Watson's appetite for data. "It can read 40 million documents in about 15 seconds," he says. "That means it can read the entire annual ophthalmic literature in less than a second."

Dr. Hildebrand says the development team envisions three features: a single-screen presentation of chart summaries and key patient information; a tool that identifies gaps in care and provides algorithms that include clinical guidelines; and a clinical decision support system that provides probabilities and optimal pathways for differential diagnoses. "This is intended to be a clinical tool, not a physician replacement," Dr. Hildebrand says.

The final piece of the software development is creating a comprehensive knowledge base of ophthalmology. "That's probably the more challenging piece to build," says Dr. Hildebrand. "That's a matter of gathering all the concepts and linking them in a knowledge tree so that that knowledge base can help drive all the other applications."

Dr. Hildebrand expects the first iteration of the Watson Health cognitive imaging tool in ophthalmology to be available by this time next year, depending on the Food and Drug Administration, which may have to review and approve some of the applications before they hit the market. The IBM commercialization team is working on that regulatory aspect, he says. RS

Professional Opportunities

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MEDICAL RETINA SPECIALIST

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Bassett Medical Center

Bassett Healthcare Network, a progressive health care network in central New York and major teaching affiliate of Columbia University, is seeking a Medical Retina Specialist to join a busy ophthalmology department based in the lovely village of Cooperstown.

KEY BENEFITS OF THIS POSITION:

- Opportunities exist for both research and teaching if interested.
- Currently there are specialists in retina, cornea, pediatrics and oculoplastics.
- The support staff is well trained and experienced in both the clinic and operating room.
- Group employed model with competitive salary
- Comprehensive benefit package, including but not limited to medical, dental, CME, relocation assistance and paid malpractice insurance

Nestled in the foothills of the Adirondack and Catskill Mountains, Bassett Medical Center is located in Cooperstown, New York, a beautiful resort village on Otsego Lake. Home to the National Baseball Hall of Fame and Museum, the Glimmerglass Opera Company, and the Fenimore Art Museum, the area also boasts many cultural and four season recreational advantages including theater, music, museums, golf, sailing, hiking, and skiing.

EEO EMPLOYER

FOR CONFIDENTIAL CONSIDERATION, PLEASE CONTACT:
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or visit our web-site at www.bassettopportunities.org

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

Can Brimonidine Reduce GA Progression?

Phase IIA trial shows potential of its neuroprotective properties for retinal disease.

Allergan's brimonidine is best known in glaucoma as the IOP-lowering agent Alphagan, but results of a Phase IIA trial reported at the American Academy of Ophthalmology meeting showed the drug, when injected into the eye in an Ozurdex-like intravitreal implant, showed some efficacy in reducing the progression of geographic atrophy in dry age-related macular degeneration.[1]

William R. Freeman, MD, distinguished professor of ophthalmology, director of the Jacobs Retina Center and vice chairman of the ophthalmology department at the Shiley Eye Center at the University of California, San Diego, reported results of the Phase IIA randomized trial of brimonidine DDS (for drug delivery system) implanted into the vitreous every six months in patients with geographic atrophy (GA) from dry AMD.

The trial compared a placebo and two dosing levels of first-generation brimonidine DDS tartrate in a 22-gauge implant at doses of 132 µm and 264 µm. The primary endpoint was change from baseline in GA area based on fundus photography, not visual acuity, and Dr. Freeman explains why: "One problem with geographic atrophy is that it continues to expand and visual acuity remains 20/20 even as the disease progresses, until it affects the foveal center. If you stop the disease from progressing, it will never affect visual acuity."

The Phase IIA trial reported that at one year, the low-dose group showed a 19-percent reduction in lesion growth rate compared to placebo, the high-dose group a 28-percent reduction, Dr. Freeman says. Here, he discusses the trial.

The mechanism of action in his own words:

The cytoprotective and neuroprotective properties of brimonidine as an alpha-adrenergic drug have been well-documented, although the exact mechanism is not fully understood. It has been shown to protect against retinal degeneration in rodent studies, and to protect against toxicity in retinal pigment epithelium cells and other types of retina cells, including neurons.

When applied as a topical drop to the front of the eye, not enough active ingredient gets to the back of the eye to protect retinal cells, and no treatment exists to halt dry AMD progression to GA. The purpose of the Phase IIA trial, and the Phase IIB trial that has already enrolled, is to determine if brimonidine can protect RPE and photoreceptors.

The thinking behind brimonidine DDS is to administer injections less frequently than the monthly schedule for anti-VEGF agents. The Phase IIB trial will use a schedule of once every three months.

The advantage of a sustained-delivery insert:

Brimonidine DDS dissolves just as the Ozurdex dexamethasone implant does. Both use the Novadur solid polymer drug delivery system, made of a PLGA intravitreal solid polymer matrix that slowly degrades to lactic acid and glycolic acid, leaving no residue in the eye.

The advantage of the implant is that it sustains therapeutic levels of drug in the retina, whereas with an injection the drug levels drop very rapidly. The implant is injected through the pars plana and floats around in the vitreous, rarely interfering with vision.

The Novadur system is already FDA-approved, but brimonidine is not approved for treatment of AMD and other retinal diseases.

The take-home of the Phase IIA trial:

The major finding is that brimonidine DDS appears to slow down the rate of progression of geographic atrophy, and that the higher dose slows it more so than the lower dose. This trial showed a definite dose response.

The other key trial finding:

The trial found the implant has a safety profile similar to Ozurdex; the only adverse effect was the expected mild irritation around the injection site.

What's next:

The Phase IIB trial, known as the BEACON trial, uses a second-generation formulation of brimonidine DDS that should deliver more drug to the retina: a dose of 400 µm of free-base brimonidine in a 25-gauge implant. If the results from BEACON are encouraging, the next step would be a large Phase III trial.

REFERENCE

1. Freeman WR. Intravitreal brimonidine drug delivery system (brimonidine DDS) in patients with geographic atrophy: A phase 2 study. Presented at: American Academy of Ophthalmology annual meeting; October 14-18, 2016; Chicago.

A Heads-up, 3D View

(Continued from page 19)

display screen is directly in front of the surgeon, but this forces the assistant surgeon to turn his or her head 90 degrees, which may make assisting with surgical maneuvers more difficult.

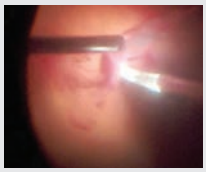
Most of us have not had the opportunity to try out this digital heads-up system. But these valuable pearls from pioneering surgeons who use it routinely can demonstrate how technology would perform in your operating room. We are stepping through a gateway toward a digital revolution in surgical visualization, and I am certainly excited for the future.

Dr. Hahn is an associate at New Jersey Retina in Teaneck. Drs. Todorich and Thanos are second-year vitreoretinal surgery fellows at Associated Retinal Consultants and Oakland University William Beaumont School of Medicine, Rochester, Mich. Drs. Ruby and Williams are partners at Associated Retinal Consultants/Oakland University William Beaumont School of Medicine, where Dr. Williams is chair of the Department of Ophthalmology.

DISCLOSURES: *Dr. Williams is a consultant for Alcon. The other co-authors had no conflicts to disclose.*

View the Video

Watch Drs. Todorich and Williams



perform primary and complex vitreoretinal surgical maneuvers including macular cases, diabetic total-retinal detachment dissections and a complex proliferative vitreoretinopathy case using the NGENUITY 3D viewing system. Available at: bit.ly/2edaYUf.

A Common Masquerade In AMD

(Continued from page 15)

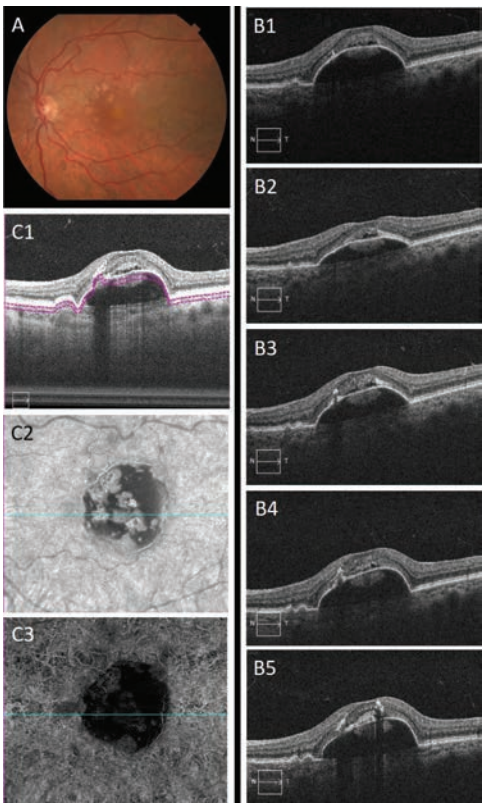


Figure 3. Color fundus photography of the left eye (A) demonstrates central pigment epithelial detachment with adjacent drusen. Spectral-domain optical coherence tomography images at the fovea (B1–B5) at baseline, and months five (after five aflibercept injections), 13 (after three more injections), 20 (after two more injections) and 26 (after three more injections), respectively, show the size of the PED and overlying subretinal fluid remain relatively unchanged. SD-OCT angiography does not show any sign of neovascularization (C1-C3).

from the RPE and trapped within a lipid-laden, hydrophobic Bruch's membrane. However, the exact mechanisms remain unproven.

Regardless, these lesions occur frequently and need to be recognized as masquerading as neovascular AMD. Moreover, these lesions demonstrate that the term "dry" AMD is a misnomer and should be avoided. Perhaps more appropriate terminology would be *non-neovascular* and *neovascular* AMD.

When subretinal fluid overlies the top of a PED, rather than on the edge of the PED, without associated intraretinal fluid, blood or a notch, then most likely the PED is not vascularized and will not respond to anti-VEGF therapy. Proceed with caution.

REFERENCES

1. Lim LS, Mitchell P, Seddon JM, et al. Age-related macular degeneration. Lancet. 2012;379:1728–1738.
2. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1432–1444.
3. Tan AC, Simhaee D, Balaratnasingam C, Dansingani KK, Yannuzzi LA. A perspective on the nature and frequency of pigment epithelial detachments. Am J Ophthalmol. 2016 Sep 13 [Epub ahead of print]
4. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO study. Am J Ophthalmol. 2009;148:43–58.
5. Sikorski BL, Bukowska B, Kaluzny JJ, Szkulmowski M, Kowalczyk A, Wojtkowski M. Drusen with accompanying fluid underneath the sensory retina. Ophthalmology. 2011;118:82-92.
6. Madjarov B, Rosenfeld PJ. Serous PEDs with associated subretinal fluid unresponsive to anti-VEGF therapy. Invest Ophthalmol Vis Sci. 2009;50:238.

Bascom Palmer Eye Institute
UNIVERSITY OF MIAMI HEALTH SYSTEM

Dr. Rosenfeld is a 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. Dr. Namavari is a medical retina fellow at Bascom Palmer.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

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

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

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

Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice. A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

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

Issue Date: June 2016
Initial U.S. Approval: 2011
June 2016

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As demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in Patients with DME

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

EYLEA® (aflibercept) Injection For Intravitreal Injection

TARGETED SCIENCE

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON

06/2016
US-LEA-1648(1)