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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.

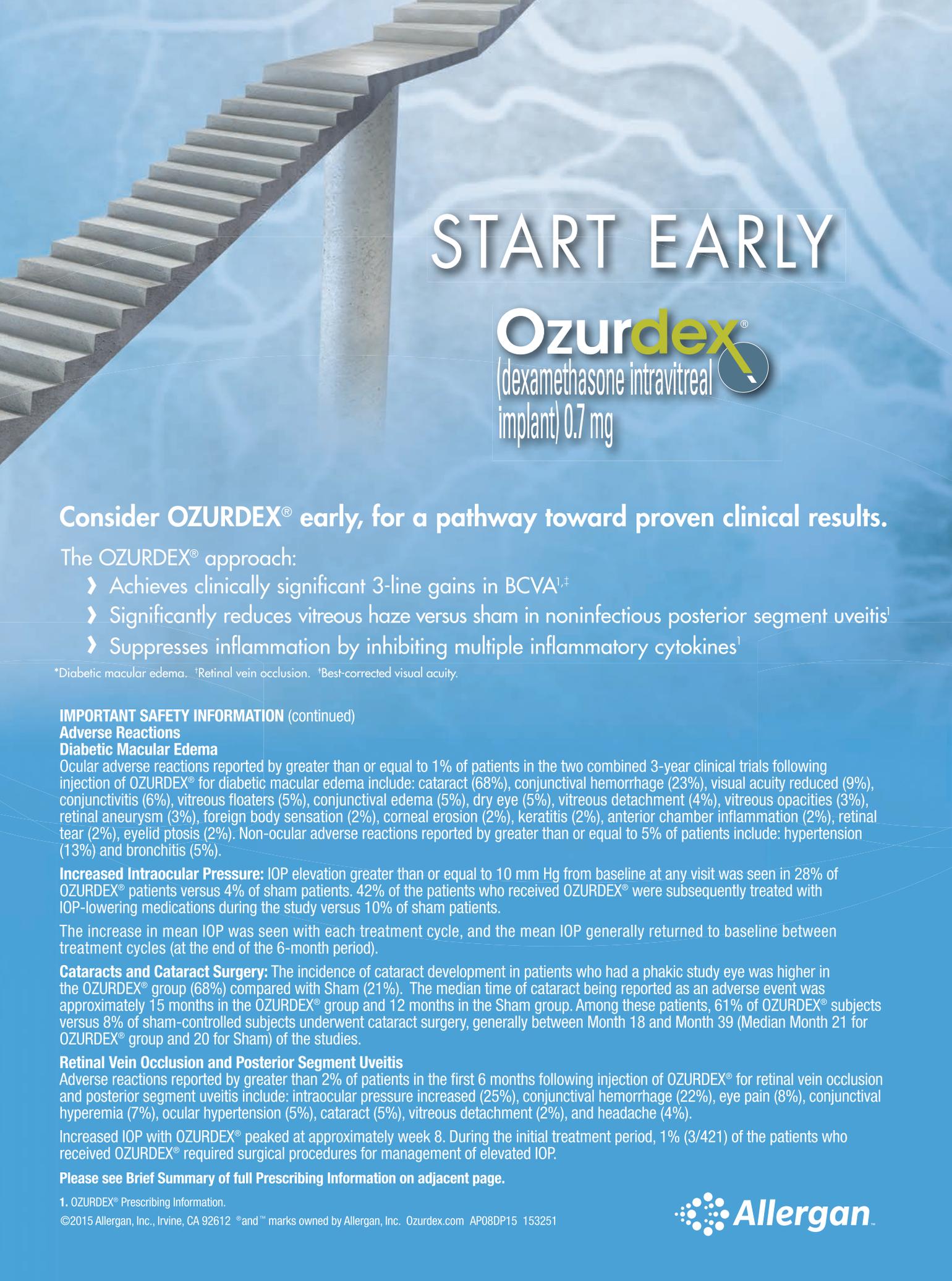
Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

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.



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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 uveitis¹
- › Suppresses inflammation by inhibiting multiple inflammatory cytokines¹

¹Diabetic 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.

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OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

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

INDICATIONS AND USAGE

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

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

Diabetic Macular Edema

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

CONTRAINDICATIONS

Ocular or Periorbital Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periorbital 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%)

¹Includes 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.

²243 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

IOP	Treatment: N (%)	
	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.

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HORV to Zika

Caring for patients with retinal diseases can be humbling. A colleague from North Dakota recently contacted me about a tragic outcome following uncomplicated cataract surgery. The patient developed severe and progressive retinal vascular occlusions and ultimately progressed to NLP in both eyes. *No light perception in both eyes.*

This syndrome has become known as HORV, or hemorrhagic occlusive retinal vasculitis, and may be associated with exposure to intraocular vancomycin. More than a dozen cases from across the United States have been reported and Andre Witkin, MD, summarizes our current, although limited, understanding of this potentially devastating clinical entity (*page 27*). If you suspect a case, please report it through the Research and Safety in Therapeutics section of the American Society of Retina Specialists website.

While such tragic outcomes are rare in the management of retinal diseases, many unknowns remain in our specialty, allowing space for improvement. To that end, this edition includes pieces by leaders in the sub-specialty fields of uveitis, ocular oncology and pediatrics who describe advances in their respective niches.

While conventional diagnostic approaches or empirical treatments often suffice in the management of uveitis and intraocular tumors, persistent or unresponsive disease activity sometimes necessitates a retinal biopsy. Prithvi Mruthyunjaya, MD, and Duncan Berry, MD,

describe optimal practices when performing a combined retino-choroidal biopsy (*page 15*).

From a treatment perspective, while corticosteroids remain an excellent option for the management of non-infectious uveitis, newer biologic options hold promise, as Thomas Albini, MD, and Chris Henry, MD, explain in their review (*page 35*).

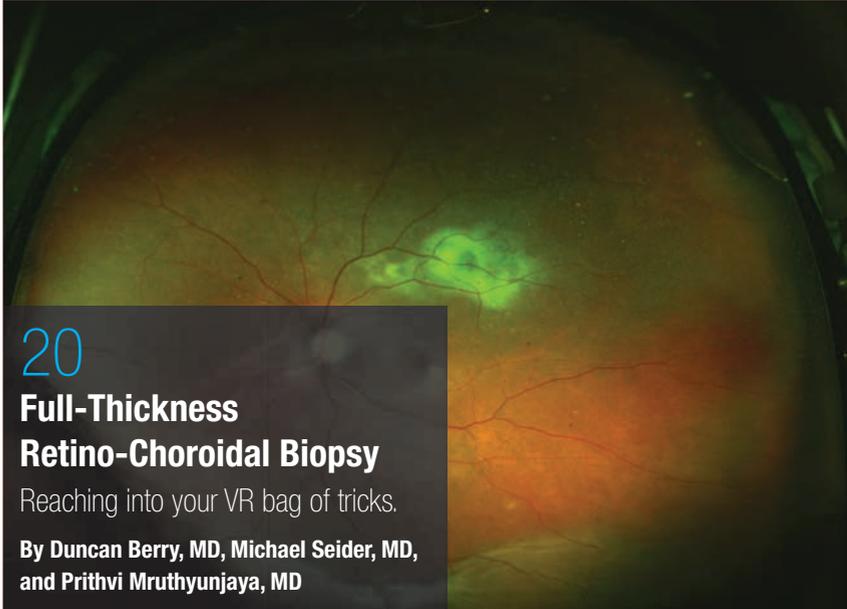
For our youngest patients, Paul Chan, MD, and Mrinali Gupta, MD, assess the value of anti-VEGF and ocriplasmin injections, how imaging advances have facilitated the expansion of telemedicine and review what we know about ocular findings ascribed to the headline-grabbing Zika virus (*page 15*).

Finally, Calvin Mein, MD, puts Diabetic Retinopathy Clinical Research Network Protocol S results into clinical perspective (*page 31*).

Entering medical school, the Dean stood before my entering class with these welcoming words: "Half of what you will learn in medical school will be outdated in 10 years and the other half may well be proven wrong." While this may be an exaggeration, it encourages us to remain vigilant observers in our practices so that we might apply our insights toward advancement of our field.

A PUBLICATION BY RETINA

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Full-Thickness Retino-Choroidal Biopsy

Reaching into your VR bag of tricks.

By Duncan Berry, MD, Michael Seider, MD,
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EVA raises the bar, but others make upgrades, too. By Gaurav K. Shah, MD, and Vincent Y. Ho, MD

IN BRIEF

- Two pioneers of competing retinal prosthetic implant systems died weeks apart in February. **John Wyatt, PhD**, 69, co-founder of the Boston Retinal Implant Project with Joseph Rizzo, died February 3. **Alfred E. Mann**, 90, founder of Second Sight Medical Products, developer of the **Argus II Retinal Prosthesis**, died February 24.

- The **ForeseeHome** AMD Monitoring Program has qualified for Medicare coverage, **Notal Vision** announced. ForeseeHome is a home-monitoring program available by prescription for patients with dry age-related macular degeneration at high risk for developing wet AMD.

- Retinal prosthesis investigator **Mark S. Humayun, MD, PhD**, has been named recipient of the National Medal of Technology and Innovation from **President Barack Obama**. Dr. Humayun developed the retinal prosthesis that eventually became the **Argus II**. He is a professor of ophthalmology, biomedical engineering and cell and neurobiology at the Keck School of Medicine, University of Southern California.

- Biotech firm **Amarantus BioScience** has requested Rare Pediatric Disease Designation from the Food and Drug Administration for its mesencephalic-astrocyte-derived neurotrophic factor (MANF) for treating retinitis pigmentosa. MANF was previously granted orphan drug designation by the FDA in December 2014.

Retinal Implant Sustains Visual Performance In Five-year Study

Individuals who have had the Argus II retinal prosthesis for five years did about as well as they had after three years with the implant, but since its commercial rollout in 2011 indications are that adverse event rates will improve in time as retina specialists get more acclimated with the implant procedure.

James Tahara Handa, MD, Robert Bond Welch Professor at Johns Hopkins Wilmer Eye Institute, reported on the five-year results of the Argus II (Second Sight Medical Products) last month at the 39th annual Macula Society meeting on behalf of the Argus II Study Group. The five-year study involved 30 subjects from the clinical trial who received the implants at 10 centers. All were blind, defined as bare light perception or worse, due to retinitis pigmentosa or other disorders before the implant.

“The five-year data looks basically the same as the three-year data in the two primary components: the adverse events rate did not change; and the performance of when people used the Argus II turned on was maintained,” Dr. Handa said. Serious adverse events totaled 24, all of which were “addressed with standard ophthalmic techniques,” and no eyes were lost, Dr. Handa says. Most complications related to the Argus II occurred in the first year after implantation.

But results of those who have

had the implant since the device was first approved for commercial use in Europe in 2011 are even more encouraging, Dr. Handa tells *Retina Specialist*.

“There were 111 patients who had the implant placed worldwide after it was approved, and the adverse event rate was actually lower for each category of possible complication since the commercial rollout than during the first year of the trial,” he says.

While the reason for the improvement in outcomes hasn't been studied, Dr. Handa says it may be attributable to three factors: surgeons are getting better with experience; Second Sight's center-of-excellence strategy that requires implant sites meet specific requirements before the company approves them to implant the device; and innovations in surgical techniques to avoid adverse events, along with the company's program to sit in during operations to address potential problems.

In the five-year study, the following percentages of patients reported improvement in these visual function tests with the Argus II turned on compared to baseline:

- Square Localization (ability to locate and touch a high-contrast target), 81 percent.
- Direction of Motion (ability to determine the direction of a high-contrast target), 50 percent.

– Grating Visual Acuity, (ability to distinguish the orientation of black and white bars of different widths), 38 percent.

As a group, performance on the Door and Line Orientation and Mobility tasks was significantly better, Dr. Handa said.

Can High-Dose Lipitor Cause Drusen Regression in AMD?

Treatment with high-dose atorvastatin has been found to cause regression of lipid deposits and improve visual acuity without progression to advanced disease in patients with dry age-related macular degeneration.

Researchers from Massachusetts Eye and Ear/Harvard Medical School and the University of Crete reported results of a Phase I/II clinical trial in the online journal *EBioMedicine*.¹ The pilot multicenter, open-label, prospective study involved 26 patients with AMD and the presence of multiple large, soft drusenoid deposits. They received 80 mg atorvastatin (Lipitor, Pfizer) daily and received a clinical workup every three months that included an eye exam, fundus photographs, optical coherence tomography and blood work.

Twenty-three subjects completed the minimum 12-month follow-up. High-dose atorvastatin resulted in regression of drusen deposits associated with vision gain (+3.3 letters, $p = 0.06$) in 10 patients. Thirteen patients were considered non-responders. No subjects progressed to advanced neovascular AMD.

“Not all cases of dry AMD are exactly the same, and our findings suggest that if statins are going to help, they will be most effective when prescribed at high dosages in patients with an accumulation of soft lipid material,” says Demetrios Vavvas, MD, PhD, a clinician scientist at Massa-

Quotable

“These data suggest that it may be possible to eventually have a treatment that not only arrests the disease but also reverses its damage and improves the visual acuity in some patients.”

- Demetrios Vavvas, MD, PhD

chusetts Eye and Ear and co-director of the Ocular Regenerative Medicine Institute at Harvard Medical School.

“These data suggest that it may be possible to eventually have a treatment that not only arrests the disease but also reverses its damage and improves the visual acuity in some patients,” he says.

The study further validates an association between lipids, atherosclerosis and retinal disease. A 2010 study involved 18 subjects with diabetic macular edema and dyslipidemia who received an unspecified dose of atorvastatin.² They showed a decrease in hard exudates and fluorescein leakage at 12 months.

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Subclinical MNV: Do We Watch or Treat?

Now that we have OCT-A, we can no longer ignore macular neovascularization in non-exudative AMD.

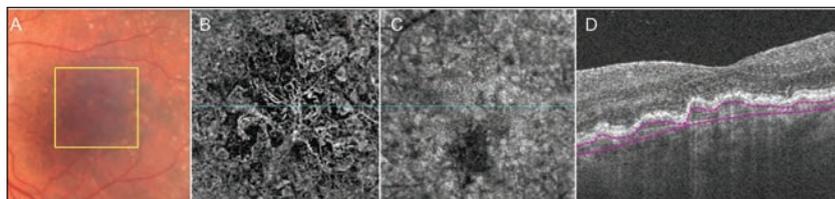
We always knew that macular neovascularization (MNV) was lurking in the back of some eyes with non-exudative (dry) age-related macular degeneration, but now we have optical coherence tomography angiography (OCT-A), so we can't ignore it any longer.

The severity scale from the Age Related Eye Disease Study (AREDS) predicts an increased risk of MNV in eyes with dry AMD when the fellow eye has exudative (wet) AMD.^{1,2} Most likely, if OCT-A had been available during the AREDS study period, subclinical MNV would have been detected more frequently in these dry AMD eyes with the higher risk of progression to exudative disease.

The difference between now and then is that we can easily detect MNV before symptomatic exudation occurs. By knowing that these lesions are present, we might be able to improve our ability to predict when exudation might occur. However, what should we do before this exudation occurs? We just don't know enough about these asymptomatic lesions to decide if early intervention is a good idea.

Confirming Subclinical Lesions

Several recent reports have used OCT-A to document the presence of asymptomatic, subclinical MNV under suspicious drusen and low-lying irregular detachments of the retinal pigment epithelium (*Figure*).³⁻⁵ OCT-A images of these “quiescent” or “subclinical” neovascular lesions confirm what has been known for quite a while. In the 1970s, Richard Green, MD, and Shirley Sarks, MD, detected signs of neovascularization



This 81-year-old man has non-exudative age-related macular degeneration in the left eye. A: Color fundus image shows drusen and pigmentary changes in the central macula consistent with non-exudative AMD. The yellow square represents the 3-mm x 3-mm scan area used to create the en face flow image shown in panel B. B: En face OCT-A flow image showing the neovascular complex under the retinal pigment epithelium. C: En face optical coherence tomography angiography structure image corresponds to the en face flow image shown in B. D: Horizontal B-scan corresponding to the blue line in B shows custom segmentation (red lines) under the retinal pigment epithelium used to create the en face flow image in panel B.

under drusen in histological specimens of eyes with AMD.

In the 1990s, Ferdinando Bottoni, MD, and colleagues and Prut Hanutsaha, MD, and colleagues identified indocyanine green angiography (ICGA) plaques in eyes with dry AMD.^{8,9} They considered these plaques to be the angiographic feature of subclinical MNV.

In a large series of 432 eyes, ICGA was performed in patients with wet AMD in one eye and dry AMD in their fellow eye, and plaques were detected in 11 percent of eyes with dry AMD.⁸ The rate of exudative conversion in these eyes with dry AMD varied from 3 to 28 percent per year,^{8,10,11} but eyes with ICGA plaques were 2.6 times more likely to develop exudative changes within 21 months of follow-up compared with eyes having normal ICGA images. Moreover, these non-exudative lesions tended to enlarge over time, causing visual distortions even in the absence of exudation.¹²

A New Era in Detection

Even though we've known for a

while that ICGA could detect eyes at risk for progression to exudation, retina specialists had not routinely performed ICGA for this purpose because of its invasive nature and the risk of an allergic or anaphylactic reaction. Moreover, ICGA is expensive, time-consuming, resource-intensive and uncomfortable for the patient. Because of these limitations, angiographic monitoring of eyes with intermediate AMD never became routine.

Now that OCT-A can detect
(Continued on page 14)



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. Roisman is post-doctoral associate in retina at Bascom Palmer.



Trouble With a Treated Tumor

The source of a scotoma came down to components of both differential diagnoses.

By Billy Pan, MD, Hassan A. Aziz, MD, and Jesse Berry, MD

A 59-year-old woman presented to the University of Southern California Eye Institute complaining of a central scotoma in her right eye. The patient first noticed flashes of light one week before the visit, with subsequent vision loss that occurred two days later. She denied any trauma, eye pain and headache, and review of systems was otherwise negative.

Medical History and Exam

The patient's ocular history was significant for choroidal melanoma of the right eye treated with proton-beam radiation 12 years previously. She had received routine annual ocular surveillance as well as systemic monitoring for liver metastases. Her most recent examination was nine months before the current visit and she was declared clinically stable with visual acuities of 20/20 bilaterally.

Fundus evaluation at that time revealed a stable, treated melanoma in the temporal periphery of the right eye, with extensive soft drusen in the macula of both eyes. An ultrasound of the right eye showed a minimally elevated lesion consistent with treated melanoma with a base diameter of 7 mm by 6 mm and height of 1.5 mm.

On the day of presentation, visual acuity had decreased to 20/400 in the right eye. Intraocular pressures, pupils and anterior segment examination were unremarkable. Fundus examination of the right eye demonstrated the previously noted drusen and treated tumor with a new area of circinate exudates along the superior and inferior arcades with

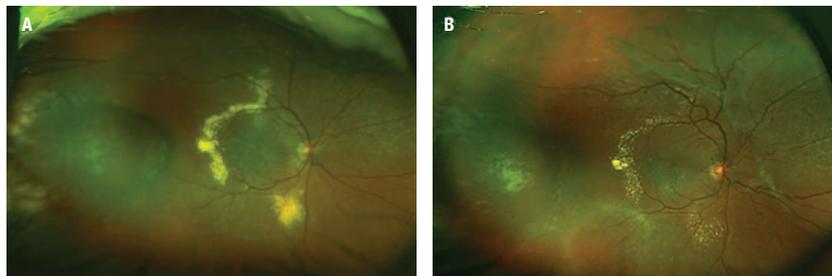


Figure 1. Widefield fundus photography of the right eye shows new onset circinate exudates along the temporal macula with associated macula edema (A). Note the treated tumor in the temporal periphery. Treated macular edema (B) is visible with resolving exudates with new onset tractional membrane formation along the superior arcades.

associated macular edema (Figure 1A). A repeat ultrasound did not demonstrate a change in the size of the tumor. Optical coherence tomography confirmed the presence of intra- and subretinal fluid in the macula (Figure 2A, page 12).

Treatment Plan

Given this patient's extensive macular edema, we initiated treatment with intravitreal bevacizumab (Avastin, Genentech). After three injections, she had recovery of visual acuity to 20/20 and OCT demonstrated complete resolution of the macular edema (Figure 2B, page 12).

However, in the subsequent months, the patient began to develop an area of fibrosis along the superior arcades with recurrent exudation (Figure 1B).

Despite treatment with sub-Tenon's and intravitreal triamcinolone, the fibrosis progressed to a macula-involving tractional retinal detachment. The patient was treated with pars plana vitrectomy, membrane peeling, retinectomy with fluid drainage, endolaser and silicone oil infusion.

Difficult Differential Diagnosis

The mainstay of globe-conserving therapy for uveal melanoma is radiation therapy, which can take the form of brachytherapy, proton-beam radiotherapy or stereotactic radiotherapy.¹ Despite great success in salvaging the eye, the collateral damage from radiation treatment can cause significant morbidity within the eye and lead to permanent vision loss.

The pathophysiology of radiation retinopathy is predominantly secondary to the loss of vascular endothelial cells. The vascular compromise manifests clinically as microaneurysms, exudates, hemorrhages, cotton-wool spots, macular edema and diffuse retinal ischemia.²

Toxic tumor syndrome arises as a result of tumor necrosis and intratumoral radiation vasculopathy after treatment, leading to ischemia, vascular incompetence and severe exudation. This in turn can result in macular edema, retinal exudates, retinal detachment, iris neovascularization and neovascular glaucoma.

With small tumors, it is easier to completely obliterate the tissue and

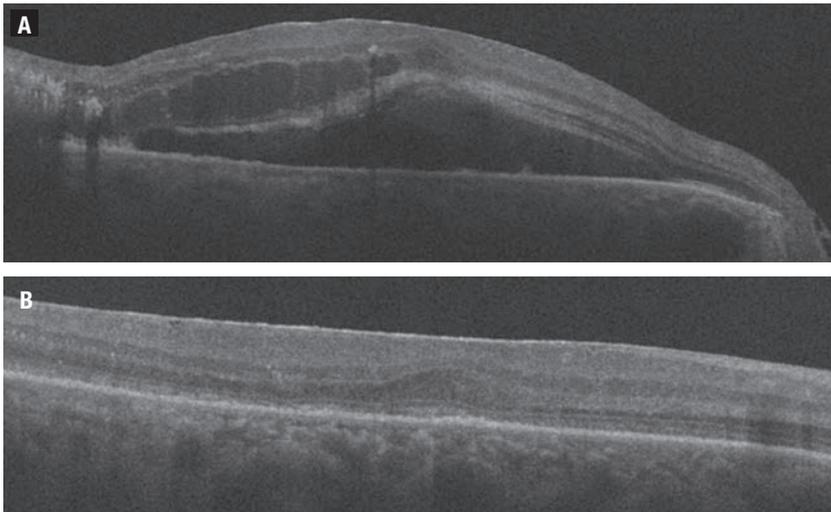


Figure 2. Optical coherence tomography of the right eye shows (A) intra-retinal and subretinal fluid with hard exudates extending to the optic nerve and (B) the resolution of fluid after a series of three monthly bevacizumab injections.

associated vasculature, resulting in an atrophic mass without metabolic activity. However, with bulky tumors, it is difficult to obtain such definitive treatment without excessive amounts of collateral damage to healthy tissue. Thus, bulky tumors may continue to release inflammatory cytokines and vascular growth factors for a prolonged period post-treatment.³

Based on the history and clinical findings, the differential diagnosis for this patient included radiation retinopathy vs. toxic tumor syndrome. Given the significant overlap between the two entities, differentiating between them can be difficult.

The time to onset of symptoms in cases of radiation retinopathy peaks at approximately two years,⁴ although late-onset radiation changes have been described even 15 years post-brachytherapy.⁵ Toxic tumor syndrome, on the other hand, does not have a well-characterized time course, but tends to have a more sudden, severe and often neovascular or proliferative presentation. We

believe that our patient had components of both diseases.

Treatment Options

In the treatment of radiation retinopathy, laser photocoagulation, photodynamic therapy, intravitreal steroids and anti-vascular endothelial growth factor agents have all been employed. Only limited literature addresses laser photocoagulation and photodynamic therapy for treatment of radiation retinopathy. Intravitreal steroids and anti-VEGF agents, however, have been well-studied and shown to be effective.⁶ Despite adequate treatment, most patients suffer permanent visual compromise once radiation retinopathy is clinically evident.

The treatment of toxic tumor syndrome can be approached in two ways. The first approach is the same as that for radiation retinopathy. However, there appears to be a treatment bias toward periocular steroids given the inflammatory basis for the condition.⁷

The second approach is directed at reducing the treated tumor burden as the source of inflammation. In the case of smaller tumors, transpupillary thermotherapy can be used to definitely halt the neovascular drive, whereas for larger tumors endoresection or trans-scleral resection may be necessary to debulk the tissue.⁸ 

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Preventing Folds After RD Repair

Temporal side down: because face-down positioning isn't foolproof or fold-proof.

With Cynthia Toth, MD

Fortunately it doesn't happen often, but rarely after a straightforward retinal detachment repair a surgeon may be unpleasantly surprised by a postoperative macular fold. Repair of these folds can be tricky and the best solution is undoubtedly prevention.

When and Why Folds Happen

These folds typically occur when enough residual subretinal fluid is focally sequestered, creating redundant retina that folds over itself under intraocular tamponade as the fluid is resorbed. Unexpected folds usually arise with bullous superior retinal detachments and are particularly problematic when the inferior edge crosses the macula.

Why? Because of gravity. Fluid settles beneath the bubble and pools at the inferior edge, which is always the location of the postoperative fold. Folds generally don't occur in inferior detachments or total detachments.

Often surgeons position a patient upright for tamponade of the retinal break causing a superior detachment. This has great potential to induce a fold under the previously described circumstances. If there is residual subretinal fluid and concern for a fold, many retina specialists may recommend face-down positioning.

Problem with Face-down

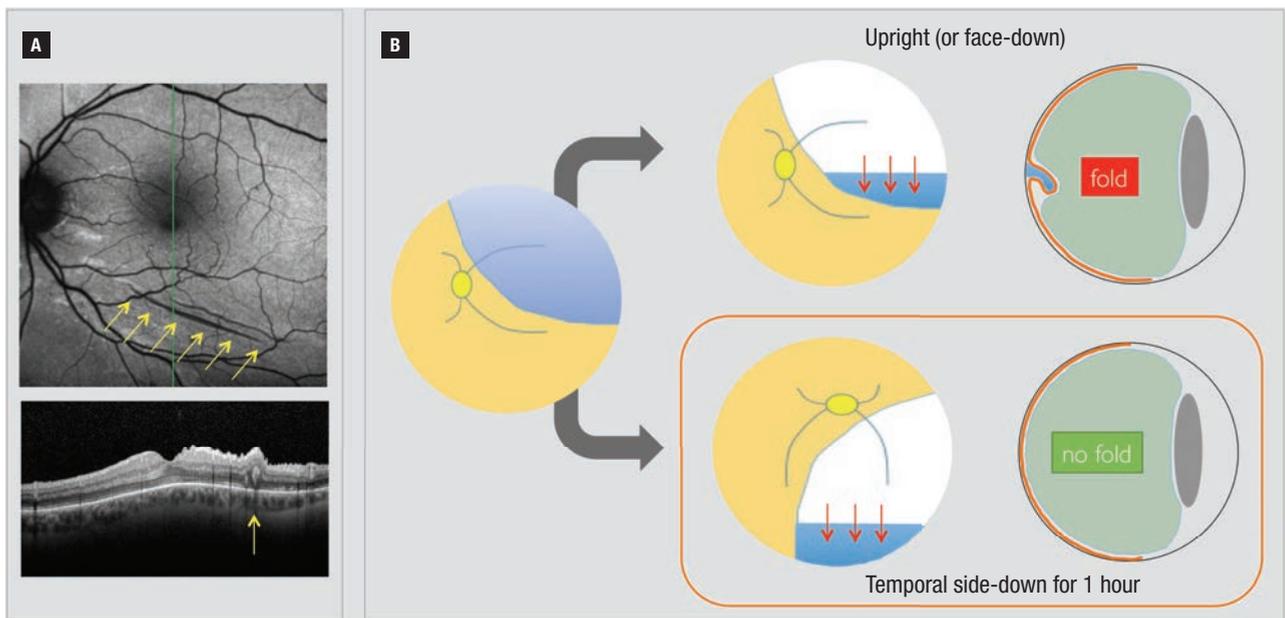
However, face-down positioning is often physically difficult for patients

Watch the Video

A video that describes postoperative macular fold repair and positioning afterward is available at: <http://goo.gl/wXXl6c>

and thus not strictly performed, especially as the patient is maneuvered in the postanesthesia care unit (PACU).

The time immediately following surgery is critical in determining the location of fluid sequestration as the retinal pigment epithelium pumps start reapposing the retina. If the patient is only partially face down during this crucial period, fluid will still be sequestered at that inferior edge and a fold may result. And even when face-down positioning is done



Postoperative fold inferior to the fovea following superior retinal detachment repair (A) is easily seen with autofluorescence and OCT imaging (yellow arrows). Although small and extrafoveal, this fold caused significant distortion and visual rotation. Following vitrectomy for repair of bullous superior retinal detachments (B), upright (or face-down if the detachment extends beyond the fovea) positioning forces residual fluid to gravitate to the inferior edge of the detachment and can promote a fold. Temporal side-down positioning for the first hour immediately postoperatively shifts fluid away from the macula to prevent fold formation.

properly under the best of circumstances, fluid can still pool if the detachment extends beyond the fovea or the apex of face-down positioning.

The Case for Temporal Positioning

Cynthia Toth, MD, a pediatric retinal specialist and retinal surgeon at Duke Health in Durham, N.C., teaches a valuable pearl with regard to patient positioning. As a pioneer of macular translocation surgery in which retinal folds and/or rotations are induced intentionally, she is well-versed in the pathogenesis of these folds.

Dr. Toth recommends first positioning the patient to lie temporal side-down for one hour. She recommends this positioning immediately at the conclusion of surgery, even before the patient is wheeled out of the operating room and into the PACU, to avoid upright positioning. The patient finds this easier than face-down positioning.

After one hour, the patient can be discharged from the PACU with standard positioning instructions to tamponade the retinal breaks (typically upright for a superior detachment). Immediate temporal side-down positioning allows sequestered fluid to shift away from the macula to the periphery, and that one hour is sufficient to allow the RPE pumps to start reapposing the macula, preventing fluid reaccumulation in the macula. In theory, a fold may still occur in the periphery, but this would likely not be visually significant and fortunately does not typically occur.

The purpose of this positioning is not to drain fluid from the retinal break but rather to shift residual fluid away from the macula as the retina is reattaching and avoid the “downward sag” of the retina. Of course, removing all subretinal fluid will also prevent folds.

But for superior detachments with any residual fluid or an inadequate view at the end of surgery to assess for residual fluid, remember this: temporal-side down for the first hour. 

*Dr. Hahn is an associate at New Jersey Retina in Teaneck. **Disclosures:** Dr. Hahn serves as a consultant for Second Sight Medical Products and Bausch + Lomb.*

Subclinical MNV: Do We Watch or Treat?

(Continued from page 10)

subclinical MNV, a new era has begun. OCT-A is a fast, safe, non-invasive and easily repeatable imaging strategy that patients can undergo at all follow-up visits. The growing availability of OCT-A will allow us to answer many of the questions surrounding these subclinical neovascular lesions, such as their incidence, their prevalence, their natural history before they become symptomatic and their response to treatment.

While we need large studies to better understand the natural history of subclinical MNV, it seems reasonable to assume that these eyes are more likely to progress to active, symptomatic forms of exudative AMD compared with eyes without evidence of MNV.

What Future Studies Can Tell Us

Further study would answer questions like: Should we follow these eyes with asymptomatic MNV more frequently, and if so, how frequently? Should we educate patients differently about their disease? Should we place greater emphasis on home vision monitoring with some of the newer devices that detect visual disturbances? Should these eyes be treated with intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors to prevent growth and exudation? If we do start treatment, then what's our endpoint for stopping, or how do we decide when to extend the treatment interval? What if anti-VEGF therapy accelerates the formation of macular atrophy by causing regression of the MNV?¹³ In clinical practice, should we treat these eyes with subclinical MNV any differently than we might treat asymptomatic eyes with early signs of exudation? Do we watch or do we treat?

We can only answer these questions by using OCT-A in large, natural history studies. Now that we have OCT-A, we can no longer ignore non-exudative neovascular intermediate AMD. 

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PEDIATRIC RETINA:

ADVANCES IN DIAGNOSIS AND TREATMENT

Widefield imaging, anti-VEGF agents and shorter instruments expand management options.

By Mrinali Gupta, MD, and R.V. Paul Chan, MD

Recent developments in retinal imaging, pharmacotherapy and surgical instrumentation have fueled progress in pediatric retina. Here, we review these advances and explore their implications for diagnosis and management of pediatric retinal disease.

Advances in Retinal Imaging

The traditional approach to documenting retinal pathology in children involved clinical examination, sometimes under anesthesia, and retinal drawings. Advances in imaging have dramatically improved our ability to capture images of the pediatric retina either at bedside or in the office. In contrast to the often brief view indirect ophthalmoscopy provides, retinal photography allows us to examine retinal features in greater detail and to assess subtle changes between visits better than fundus drawings could.

Widefield fundus cameras such as the RetCam (Clarity Medical Systems) enable handheld imaging and fluorescein angiography of infants in the clinic and at bedside. RetCam

achieves 130° of mydriatic retinal imaging using a handheld contact camera system with a fiberoptic cable. While well-suited for retinopathy of prematurity, use of the camera in older infants and children typically requires anesthesia. Additionally, imaging of the far periphery requires peripheral sweeps or montaging.

The Optomap (Optos) ultra-widefield imaging is a non-contact, non-mydriatic system that allows rapid, office-based photography and FA of a wider retinal area (200°). Optomap imaging has been reported in patients as young as 5 years with a number of pediatric retinal conditions,^{1,2} and we have used it on some children as young as 3 years (*Figure 1, page 16*). Additionally, Optomap

ultra-widefield FA-guided panretinal photocoagulation has been reported in patients with conditions such as Coats' disease and familial exudative vitreoretinopathy.¹ Recent studies describe a “flying baby” technique of

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DISCLOSURES: Dr. Chan is a consultant for Alcon and Allergan.

holding premature infants upright onto the Optomap interface for ROP imaging,³ but the technique is technically challenging and typically does not work in babies older than 6 months.⁴

The Heidelberg Spectralis ultra-widefield imaging module (Heidelberg Engineering) uses a camera attachment to capture non-contact-based, high-contrast images of up to 102° of the retina. This system has been used for imaging of babies under anesthesia at 33 weeks gestational age through 12 months. The lens can be rotated 90° for imaging in supine patients.⁴ While less portable than the RetCam and with a smaller widefield than Optomap, Spectralis offers the ability to use additional modalities such as optical coherence tomography and indocyanine green angiography.

In the current pediatric retinal imaging paradigm, very young infants such as neonates undergoing ROP screenings can be imaged using the RetCam system, while children 3-5 years of age and older can often cooperate with office-based Optomap imaging. Imaging of older infants and children younger than 3-5 years generally requires examination under anesthesia, usually with the RetCam.

Take-home Point

Insights gleaned from advances in pediatric retinal imaging have impacted our understanding and diagnosis of pediatric retinal disease. These advances, coupled with tools for computer-based image analysis, also have implications for telemedicine. These imaging advances, along with the potential of pharmacologic vitreolysis and the growing role of anti-VEGF agents are moving forward our ability to treat pediatric retinal disease.

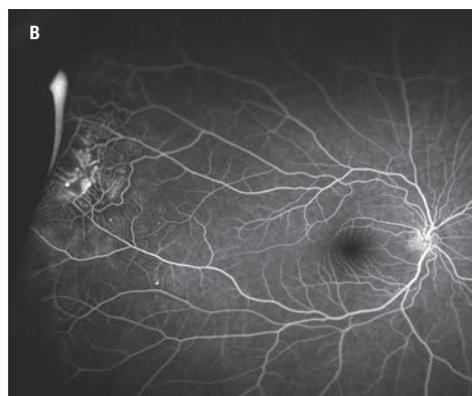
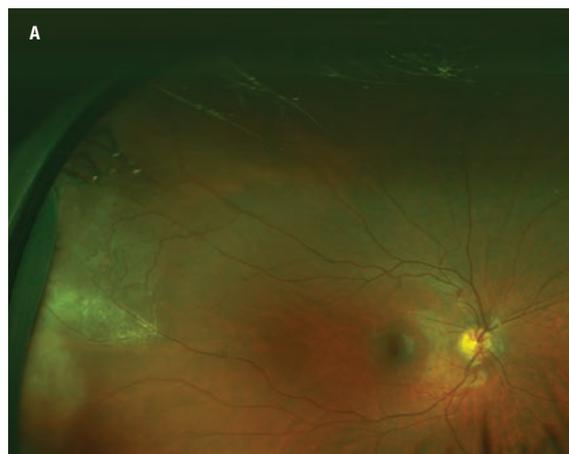


Figure 1. Fundus photograph of an 11-year-old patient with Coats' disease reveals temporal exudation and telangiectasias (A). Fluorescein angiography reveals light-bulb telangiectasias (B at 1 minute, 23 seconds; C at 5 minutes, 18 seconds).

Imaging Systems on the Horizon

The PanoCam LT (Visunex Medical Systems) widefield handheld system is now approved in the United States and offers a more compact, wireless, contact-based system for newborn widefield imaging (130°).

The 3nethra Classic (Forus Health) is a compact, table-top, non-mydratic digital imaging system offering a 40-45° field of view. The 3nethra neo is a lightweight, non-wireless but compact, contact-based system for high-definition imaging with a 120°

field of view. This system is well-suited for ROP imaging and offers mounting capabilities. Both Forus systems are affordably priced, compact and enable secure transmission of images to a cloud-based system, making them particularly well-suited for telemedicine.

Impact of Widefield Imaging

The recent widespread availability of widefield imaging systems with FA capabilities such as the RetCam has brought to light the utility of FA for ROP diagnosis. Recent studies have suggested that compared to color fundus photographs alone, FA resulted in increased sensitivity for diagnosis of stage 2 or worse ROP, stage 3 or worse ROP, pre-plus or worse disease and type 2 or worse ROP,⁵ but did

not improve diagnosis of the macular center and only marginally improved sensitivity for zone diagnosis.⁶ These findings have important implications for the use of FA in ROP surveillance as well as in remote, imaging-based, telemedicine screening.

Based largely on FA features and clinical course, Audina Berrocal, MD, and colleagues have described ROPER (ROP vs. FEVR), in premature infants who exhibit retinal findings more characteristic of FEVR than ROP. The distinguishing FA features in ROPER include irregular sprouts of vascularization at the vascular/avascular junction (vs. the more uniform advancing front of ROP), distinct pruning of vessels, pinpoint areas of hyperfluorescence and segmental areas of vascular leakage.⁷ The diagnosis of ROPER may have implications for management because, like FEVR, these patients may exhibit a more unpredictable and long-term course than those with ROP.

Improvements in peripheral retinal imaging in patients with FEVR have led to a proposed revision of the original five-stage FEVR classification scheme.⁸ Michael Trese, MD, and colleagues reported a wide range of previously undescribed clinical features from widefield imaging of 174 eyes with FEVR:⁸ anatomical features such as circumferential peripheral vessels, venous and arterial tortuosity; late-phase disc leakage; central and peripheral telangiectasias; capillary anomalies and capillary agenesis; and functional features such as venous-venous shunting, delayed arteriovenous transit and delayed or absent choroidal perfusion.

They reported that these findings have implications for the classification and prognosis of FEVR. For example, widefield imaging revealed a subset of stage 2 FEVR patients who exhibited

Ocular Manifestations of the Zika Virus

Recent months have seen a rapid spread of the Zika virus (ZIKV) through Brazil and elsewhere in the Americas, and ZIKV infection in pregnant women is thought to potentially be associated with microcephaly in the infants born to these women.

A recent study on 29 infants with microcephaly and presumed congenital ZIKV infection revealed a high prevalence of ocular abnormalities (17 eyes [29.3 percent] of 10 children [34.5 percent]).³² These abnormalities included retinal and chorioretinal atrophy in 64.7 percent of eyes, optic nerve abnormalities (47.1 percent), bilateral iris coloboma (11.8 percent) and lens subluxation (5.9 percent).

This high prevalence of severe ocular abnormalities in infants with presumed congenital ZIKV infection not only suggests a need for routine ophthalmologic evaluation in all infants with potential congenital ZIKV infection, but also poses a significant public-health concern.

fluorescein leakage without clinical exudation (stage 2a in the original scheme), and this population seemed to be at high risk of progression to retinal detachment (stage 3).⁸ The proposed revised staging system includes angiographic leakage, even in the absence of clinical exudate, as a criterion for stage 2b FEVR. Similarly, widefield angiography revealed that some patients with early FEVR exhibit anomalous intraretinal vascular patterns rather than an avascular retinal periphery, so these features would be included in the revised stage 1. A subset of the stage 1 patients also exhibited angiographic leakage, which can result in exudation limiting the ability to treat. The revised stage 1 is now sub-categorized as stage 1a and 1b, reflecting those without or with clinical exudate or fluorescein leakage. This proposed re-classification has therapeutic implications, as the authors recommend treatment for the now-broadened stage 2b and the newly conceived stage 1b FEVR.⁸

In a separate study, Dr. Trese and colleagues found that up to 58 percent of asymptomatic relatives of individuals who have FEVR exhibited subtle stage 1 and 2 FEVR features on widefield FA, and 35 percent exhibited stage 2 FEVR. This led them to recommend clinical and widefield imaging screening of family

members of patients with FEVR.⁹

Potential for Telemedicine

Advances in retinal imaging and image analysis tools have complemented the development of telemedicine in retina, particularly for ROP. In the United States, only 29 percent of neonatal intensive care units provide both ROP diagnosis and treatment capabilities,¹⁰ and the need is even more striking worldwide.

Several studies have shown telemedicine-based remote digital fundus imaging (TM-RDFI) has a high level of accuracy for detecting clinically significant ROP,¹¹⁻¹³ although some studies have demonstrated lower sensitivities for diagnosis of Type 2 or worse ROP or stage 3 disease.¹⁴ The *2015 Joint Technical Report from the American Academy of Pediatrics, the American Academy of Ophthalmology and the American Association of Certified Orthoptists* noted that, although the data does not yet support TM-RDFI replacing traditional indirect ophthalmoscopy, moderate evidence supports its use “to identify patients with clinically significant or referral-warranted ROP for ophthalmic evaluation and management.”¹⁴

To facilitate telemedicine-based ROP surveillance, the Imaging and Informatics in Retinopathy of Prematurity (i-ROP) consortium has created

a database of all ROP infants screened at 12 major academic institutions worldwide.¹⁵ The large repository of images in the database, in combination with their “reference standard diagnosis,”¹⁵ has become a major research tool in ROP.¹⁶ Approximately 2,500 image sets and “reference standard diagnoses” from this database have been used in a collaboration of the i-ROP consortium and the Global Education Network for Retinopathy of Prematurity (GEN-ROP) to create a web-based ROP tele-educational system that has been validated in the ophthalmology resident population to improve accuracy of ROP diagnosis.¹⁷ This validation tool may have utility in certification of telemedicine experts and in training ophthalmologists.

A major challenge in ROP diagnosis is lack of agreement amongst experts on diagnosis of plus disease.¹⁸ The ROPTool is a computer program that traces retinal vessels to quantify vascular dilation and tortuosity. Studies have suggested that the ROPTool and other available image analysis tools can aid in the diagnosis of plus disease.¹⁹

A limitation for computer-based image analysis in ROP, however, has been poor inter-expert agreement and imperfect reference standards.²⁰ The i-ROP consortium’s computer-based imaging analysis system assessed a number of image features against the reference standard diagnoses and developed an algorithm based on acceleration of all vessels in a circular cropped image with a radius of 6 disc diameters (Figure 2), which achieved 95-percent accuracy in diagnosis of plus vs. no-plus, as well as in diagnosis of plus, pre-plus or no-plus disease.¹⁶

Beyond ROP, interest in universal telemedicine eye screening of neonates has also grown in recent years.

Newer Instrumentation and Pediatric Vitreoretinal Surgery

The pediatric eye differs significantly from the adult eye because it is not only smaller, but the lens is relatively large and intraocular structures relatively closer in proximity. Moreover, the sclera is thinner and potentially more prone to sclerotomy leaks, the non-synergetic vitreous is thicker, and posterior vitreous detachment induction can be challenging.

The Alcon 25+ gauge short instruments are shorter and stiffer than standard instruments. These short instruments may be better-suited for the smaller space of the pediatric eye and confer theoretically less risk of lens trauma. The stiffness of the instruments can enable surgical maneuvers through thin sclera and thick vitreous with potentially less risk of instrument bending. The 25+ gauge short packs come with a sutured-in infusion.

The utility of 27-gauge instrumentation with faster cut rates (7,500) for pediatric retinal surgery remains to be determined. The smaller instrumentation may be well-suited for smaller eyes and have less risk of causing postoperative sclerotomy leaks, but the greater flexibility of the 27-gauge system may pose some challenges. It is also unclear whether the higher cut rates will efficiently cut the pediatric vitreous. Further studies of the 27-gauge systems in pediatric vitreoretinal surgery are needed.

Darius Moshfeghi, MD, is leading the Newborn Eye Screen Testing (NEST) study to evaluate the role of universal eye screening in a U.S. population.²¹

Role of Anti-VEGF Agents

Some pediatric retina specialists are increasingly advocating for the use of anti-VEGF therapy for select cases of ROP, especially those with posterior disease, as well as those with media opacity or poor dilation. While this represents an important addition to our arsenal of available therapies, a number of questions remain.

The Bevacizumab Eliminates the Angiogenic Threat for ROP (BEAT-ROP) study demonstrated the efficacy of bevacizumab (Avastin, Genentech) vs. laser for treatment of zone I, stage 3 with plus disease or posterior zone II, stage 3 with plus disease.²² Anti-VEGF agents are attractive for ROP because they may limit visual field loss from laser, may work faster and may allow the posterior retinal and foveal avascular zone to develop in young children. Anti-VEGF drugs can be administered through media opacity and do not require general

anesthesia. Additionally, patients with anti-VEGF therapy may develop less refractive error than those treated with laser.²³

However, the systemic effects of anti-VEGF agents on the development of neonates are still unclear. The risk to the developing brain may be particularly high due to impaired blood-brain barrier function. Local adverse events include the risk of re-activation and even “ROP crunch” due to rapid regression and contraction of fibrovascular membranes. The rate and time to recurrence of ROP may be less predictable with anti-VEGF agents than with laser, and late recurrences after anti-VEGF therapy have been reported.²⁴

Two recent studies on eyes with ROP treated with anti-VEGF therapy noted abnormalities in FA, some of which persisted long after therapy. They included peripheral avascularity, abnormal peripheral vascular patterns, perivascular leakage, and/or absence of the foveal avascular zone.^{25,26} These studies have raised concerns regarding the potential effect of anti-VEGF therapy on retinal vascular development. Further studies are

needed to determine the long-term ocular and visual implications of these FA features. Neonates treated with anti-VEGF agents may require prolonged follow-up with FA, although the optimal timing remains unclear.

The ideal timing of the injection as well as the ideal anti-VEGF agent and dosing also remain unclear. Most studies of anti-VEGF agents for ROP have used bevacizumab, although limited recent studies have also described use of ranibizumab (Lucentis, Genentech), which has a shorter half-life and potentially fewer systemic effects.²⁷ A recent small retrospective series reported similar outcomes with both agents,²⁸ although another reported a high recurrence rate (83 percent) with ranibizumab.²⁹ Controversy also remains over whether intravitreal anti-VEGF monotherapy, laser monotherapy or combination laser and intravitreal anti-VEGF therapy is best.³⁰

The Phase III RAINBOW study (Ranibizumab compared with laser therapy for the treatment of Infants Born Prematurely with Retinopathy of Prematurity) is designed to answer some of these questions. The study will compare ranibizumab (0.1 mg or 0.2 mg) and laser for zone I ROP with plus disease, zone I ROP with stage 3 disease, zone II, stage 3 plus disease, or aggressive posterior ROP.

Ocriplasmin In Pediatric Vitreoretinal Surgery

Recent studies have raised the question of whether ocriplasmin (Jentrea, Thrombogenics) has a role in facilitating posterior vitreous detachment induction during pediatric vitrectomy. A recent study compared intravitreal ocriplasmin vs. sham injection prior to vitrectomy and found no significant differences in adverse events or in efficacy of PVD



Figure 2. The i-ROP computer-based image analysis system has demonstrated efficacy in diagnosis of plus vs. no plus disease and plus vs. pre-plus vs. no plus disease from fundus photos (A) through an algorithm that calculates acceleration of all vessels (B) in a circular cropped image with radius of 6 disc diameters (C).

induction. The investigators noted improved ease of vitrectomy in most ocriplasmin-treated eyes.³¹ Further studies of ocriplasmin with larger patient numbers and more refined and objective endpoints are necessary. 

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FULL-THICKNESS RETINO-CHOROIDAL BIOPSY: REACHING INTO YOUR VR BAG OF TRICKS

Small-gauge instruments may make this procedure more feasible for vitreoretinal surgeons.

By **Duncan Berry, MD, Michael Seider, MD, and Prithvi Mruthyunjaya, MD**

There are few procedures that, at just their mere description, can give any of us real trepidation and pause. Reaching in and cutting out a piece of the retina in order to diagnose a potentially vision- or life-threatening condition may be one of them. However, with the adaptation of smaller-gauge instrumentation to provide better tissue level control and improved globe stabilization with valved cannulas, full-thickness retino-choroidal biopsy (FTRCB) may have just become a more feasible intervention for the vitreoretinal surgeon.

Why Do It?

Several indications exist for invasive biopsy of the posterior segment of the eye. They include persistent uveitis of unknown cause and to obtain samples of some intraocular tumors. Usually a diagnostic vitrectomy, for purely vitreous-involving disease, or transvitreal fine-needle aspiration biopsy (FNAB), for choroidal lesions, is sufficient. However, FTRCB may be indicated in exceedingly rare instances with full-thickness retina/subretinal involvement and where conventional methods fail to yield a diagnosis, when malignancy or infection is suspected, or a histologic specimen will alter the treatment plan.

For many of our patients with posterior or panuveitis, we can make a diagnosis clinically with non-invasive ancillary diagnostic tests. However, an FTRCB may be indicated in a

handful of specific instances.

After taking a comprehensive ocular and systemic history, these challenging situations require we utilize all available diagnostic modalities. Fluorescein angiography, B-scan ultrasonography, indocyanine green angiography and high-definition ocular coherence tomography may all provide potentially important diagnostic information. Moreover, systemic blood work for autoimmune, neoplastic and infectious etiologies is often necessary, and systemic computed-tomography and/or magnetic resonance imaging may also be indicated.

Vitreoretinal Lymphoma

In those patients with obvious retina/subretinal lesion and where diagnostic measures fail to confirm a diagnosis, the patient is unrespon-

sive to therapy, or if the fellow eye is threatened despite seemingly appropriate therapy, one may

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Disclosures: Dr. Mruthyunjaya has relationships with Allergan, Optos and Santen. Drs. Berry and Seider have no relationships to disclose.

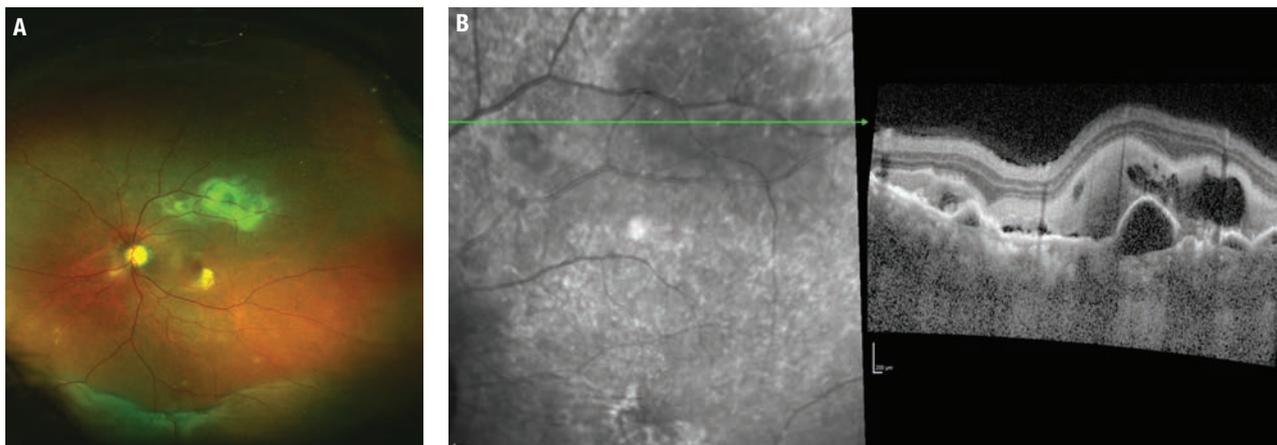


Figure 1. On exam (A), this patient had an inferior retinal detachment, shallow submacular fluid associated with hard exudates and subretinal fibrosis. Creamy subretinal infiltrates along the superotemporal arcade were also visible. Optical coherence tomography (B) with a cut through the superotemporal arcade showed dilated choroidal vasculature, multiple pigment epithelial detachments and hyperreflective subretinal infiltration.

consider a FTRCB procedure to help guide treatment.¹⁻⁵

Between 2.3 and 2.5 percent of all patients with an initial presenting diagnosis of uveitis have been eventually diagnosed with a malignancy, with primary vitreoretinal lymphoma (PVRL) representing the most common neoplastic masquerade syndrome.^{6,7} In cases where PVRL is suspected, brain/spinal MRI and lumbar puncture may help identify coexisting central nervous system disease. For both diagnostic and therapeutic purposes, a vitreous specimen can be sent for cytology, flow cytometry, IL-10/IL-6 ratios and IgH gene rearrangements.⁸

Nevertheless, in some cases, a paucity of vitreous cells can impede a diagnosis by vitrectomy alone; the patient may have a more retino-invasive form of lymphoma that may masquerade as posterior uveitic condition; or have been non-responsive to ongoing treatments. These cases may warrant a tissue diagnosis necessitating a retinal specimen.⁹

Another scenario where a FTRCB may be required is if an infectious

cause of posterior or panuveitis is suspected and the results of the biopsy will alter the treatment plan. Despite knowing the classic patterns of presentation of viral or bacterial retinitis, some conditions may produce an atypical clinical picture especially in immunocompromised patients.

Polymerase chain reaction analysis of the aqueous and/or vitreous is widely available, with good positive and negative predictive values.¹⁰ However, cases have been reported where this may not yield an answer and a FTRCB may be necessary to determine the proper course of treatment.

Perhaps the best way to both demonstrate the indications for this procedure and to discuss the finer points of performing the surgery itself is to consider the case of a patient who presented to our clinic.

Case: Exudative Retinal Detachment With Choroiditis

A 70-year-old woman presented with a chronic-appearing exudative retinal detachment associated with

choroiditis and a focal area of creamy subretinal infiltrates in the left eye. She had no light perception in the fellow eye due to a previous complicated rhegmatogenous retinal detachment. Her medical history was significant only for idiopathic proteinuria, for which she was taking oral prednisone.

On exam, no iritis or vitritis was present. We noted a chronic appearance to the inferior subretinal fluid (SRF), shallow submacular fluid associated with hard exudates and subretinal fibrosis. Creamy subretinal infiltrates along the superotemporal arcade were also evident.

OCT (*Figure 1*) demonstrated significant choroidal thickening with dilated choroidal vasculature, diffuse

Take-home Point

Full thickness retino-choroidal biopsy (FTRCB) has been difficult to perform, but with the emergence of small-gauge instruments, this procedure may be becoming more feasible for vitreoretinal surgeons. This article discusses indications and steps involved in performing FTRCB.

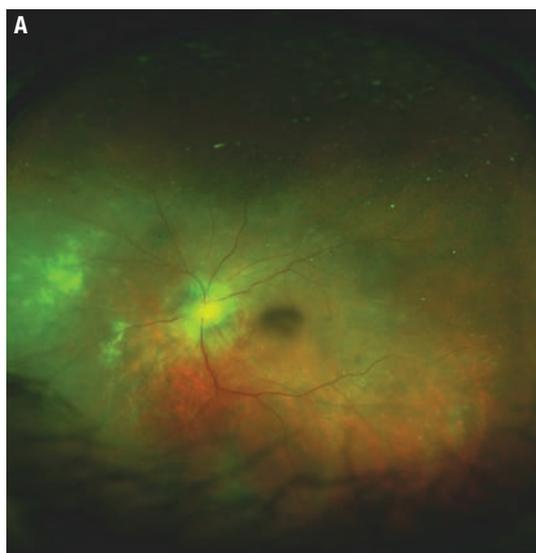
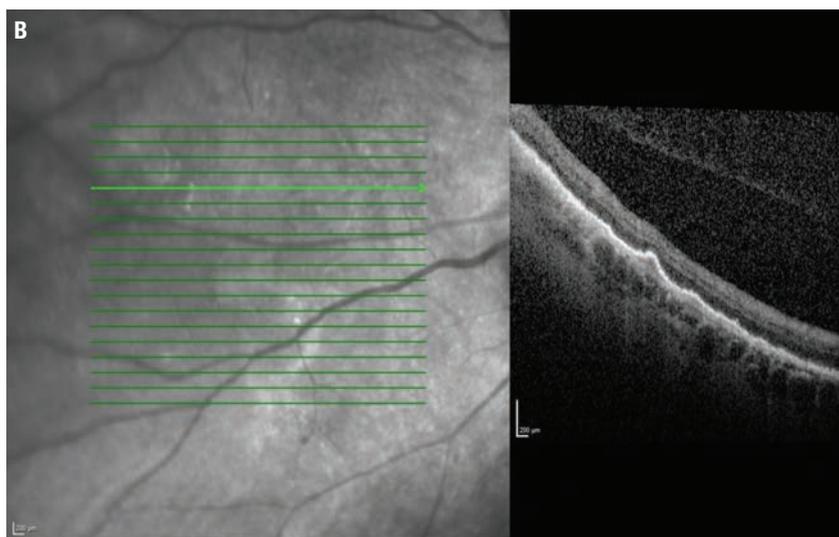


Figure 2. This 62-year-old woman also required full-thickness retino-choroidal biopsy (FTRCB). She presented with subacute vision loss and was found to have active creamy yellow/white infiltrates in the nasal/inferior midperiphery (A). On optical coherence tomography (B), the finding appeared to be largely confined to the subretinal space and to be less impressive than the previous case. She had rapidly progressive vision loss in both eyes over a few weeks and an entirely negative workup, which prompted the FTRCB.



SRF extending inferiorly, multiple pigment epithelial detachments and hyperreflective subretinal infiltration under the superotemporal arcade. Fluorescein angiography imaging showed patchy choroidal filling followed by multiple hyperfluorescent points with late leakage and staining of subretinal fibrosis. No signs of vasculitis or papillitis were present.

A comprehensive systemic workup was within normal limits except for the aforementioned proteinuria. A diagnostic vitrectomy and transvit-

real FNAB also did not yield a diagnosis. At that point the patient had also been unresponsive to a six-week course of systemic corticosteroids.

So here we are with a patient who is monocular, has a vision-threatening process that was unresponsive to treatment and in whom conventional methods failed to yield a diagnosis. We decided to perform a FTRCB with the hope that a histologic specimen would help make a definitive diagnosis and guide further treatment.

Planning, Planning, Planning ...

FTRCB is one of the more challenging retinal procedures you may perform, so meticulous planning is an absolute necessity. Here are key steps involved in the process:

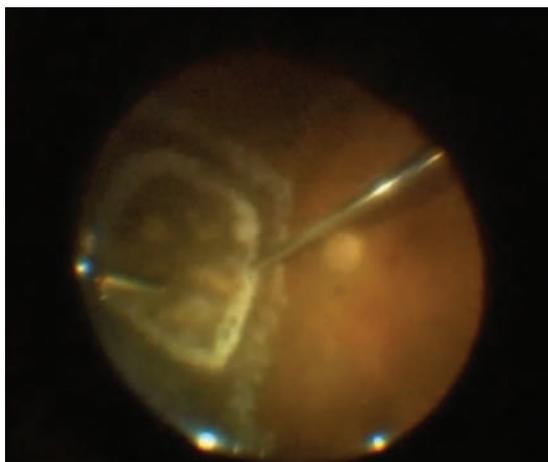
- **Communicate with your pathologist.** You'll want to discuss storage media and transportation means for your specimen, and you may even consider asking the pathologist to be present in the operating room to confirm you're obtaining an adequate specimen. (We've had cases where the specimen was "lost in processing.") You may also want to consult with the pathologist when choosing a biopsy site (more on this later).

- **Do you have all the right tools and toys?** Certain instruments are crucial for performing a FTRCB. We all have several instruments at our disposal that can cut posterior segment tissue, but it is important to achieve a biopsy with minimal specimen damage. We have found vertical scissors with a sharp tip (automated or manual) best suited to cutting the retina in a precise manner without losing valuable tissue as with a vitreous cutter, although we have used 25-gauge cutters for this maneuver.

You will also want to make sure you have intraocular forceps, a working diathermy and a lighted pick on hand. We routinely will place a chandelier light to allow for adequate illumination when performing bimanual maneuvers. Finally, we prefer valved cannulas as they allow better control of intraocular pressure, which is particularly important in these cases because achieving hemostasis can be a challenge.

- **Choose the ideal biopsy site.** Aside from appropriate patient selection, choosing the right biopsy site is conceivably the most important step. The site should involve the

Figure 3. Intraoperative still image of the biopsy site shows where endolaser was applied to barricade the nasal area up to the far periphery. A more confluent circle of laser was applied to immediately surround the area of retinitis and deep endodiathermy was applied to the inner laser barricade to help initiate the retinectomy.



pathology of interest, but selecting an area that involves both the abnormal tissue as well as adjacent normal tissue is important so that the pathologist can compare both. Also, selecting an “edge” of abnormal tissue may be important for identifying areas with active disease, especially in suspected choroidal lymphoma. These tumors may consist largely of necrotic tissue, so specimens ideally should include the deeper part of the lesion, near the choriocapillaris where viable lymphoma cells are most likely to be found.¹¹

When choosing a biopsy site, consider potential complications. Often, the pathology in posterior uveitis, primary vitreoretinal lymphoma and choroidal lymphoma involves the posterior pole. Remember that if a major artery or vein crosses the area of interest, it must be cauterized, which will cause non-perfusion distally. You will also want to be in an area that facilitates tamponade. This is especially important as larger biopsies inevitably cause biopsy-site fibrosis and some degree of proliferative vitreoretinopathy. So an inferior site (especially if anterior) is less desirable.

• **Beware the unavoidable.** Consider specific intraoperative chal-

lenges before surgery. Remember that in these cases, the eye is usually injected, the conjunctiva bleeds a lot, posterior synechiae may be present and media opacity issues may arise—all of which you should account for in your planning (*Figure 2*).

The Procedure Itself

Once you choose a biopsy site and you are ready to proceed, start by performing a thorough vitrectomy. If possible, peel the hyaloid off the site of interest to facilitate the biopsy and prevent postoperative traction and fibrosis. Complete vitrectomy is also important to allow for adequate tamponade and possibly prevent complications associated with PVR.

Keep in mind that patients often may have already undergone diagnostic vitrectomy before the chorioretinal biopsy surgery.

If the patient has significant exudative retinal detachment, consider performing an anterior drainage retinotomy and flattening to posterior retina (which may include the biopsy site) with perfluorocarbon. You cannot take retina, retinal pigment epithelium and choroid in an area of retinal detachment unless it is flattened first.

When you are ready to begin the actual biopsy portion, start by diathermizing large vessels on all sides of the biopsy site and consider diathermizing an outline of the biopsy site to prevent bleeding. Remember, this is not just a retinal biopsy, but also a retino-choroidal biopsy, so be sure to put moderate posterior pressure on your needle-tip cautery during this step so as to also cauterize choroidal vessels.

This brings you to the point where you are ready to excise the tissue, but there are a couple things to consider before you actually start cutting. Bimanual technique is helpful for an appropriate biopsy, so consider placing a chandelier, if available. Also, as hemostasis is one of the biggest

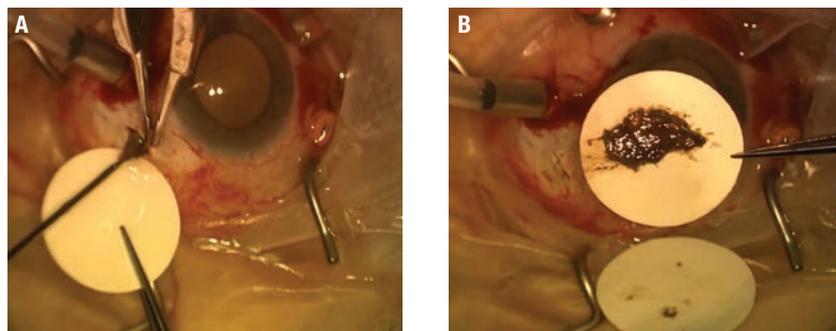


Figure 4. The sclerotomy has been enlarged, cannula removed and infusion line pinched, and the filter paper held by the assistant is ready to receive the specimen as it is removed from the eye (A). Then the intact retino-choroidal section is flattened and spread on the filter paper (B).

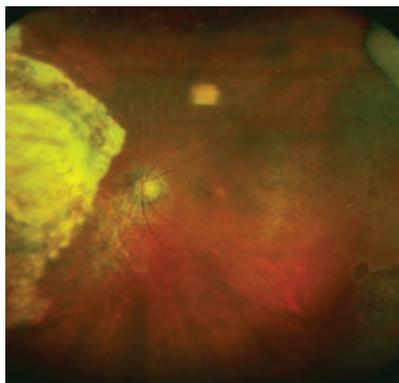


Figure 5. At six months postoperatively, extensive laser barricade is still evident. This patient had some residual hemorrhaging immediately after the biopsy, but it resolved.

challenges you face during the biopsy, elevate IOP to 50 mmHg or greater just before you start cutting the specimen.

When making cuts to outline the tissue of interest, be sure to advance the scissors probe tip (and push slightly) posteriorly to make cuts through retina, RPE and choroid. This usually requires multiple passes. Also, intraocular forceps and bimanual technique are essential to provide upward or lateral traction on the tissue so the scissors can cut at the exact outlined edge. To prevent specimen dislocation within the vitreous chamber, consider leaving a small area of specimen attached to adjacent tissue until you are ready to make the final cut in all three layers (Figure 3, page 23).

Removing the Specimen

Just before removing the specimen, remove the cannula (if used) and enlarge the sclerotomy through which you plan to extract the specimen. A small sclerotomy will cause significant tissue damage during specimen removal. However, beware that a large sclerotomy in the presence of elevated IOP can create

significant turbulence that can easily sweep your specimen into the vitreous cavity.

That said, as your last step before removing the specimen, pinch your infusion to prevent excessive turbulence. Finally, have filter paper and an assistant ready to “catch” the specimen as you remove it from the eye (Figure 4, page 23). Usually the specimen can be removed en-bloc, but sometimes the retina and RPE/choroid come out in separate layers.

Apply retinopexy around the biopsy site, check for peripheral breaks and place tamponade. We typically use silicone oil for tamponade, although that can depend on the specifics of the case and location and size of the biopsy.

Potential Complications

Retino-choroidal biopsy is not a routine procedure and does carry significant risks, the most notable, and perhaps most controversial, of which is the contention that surgical manipulation of malignant lesions promotes metastases. This has not been observed in the limited number of published case series, although most of these series have had relatively short follow-up periods.^{1,3,12}

Patients undergoing FTTCB are at risk of complications accompanying other types of vitreoretinal surgery—cataract, vitreous hemorrhage and retinal detachment. The data on postoperative complications after FTTCB is somewhat limited because this is a rarely performed procedure and the number of case series in the literature is limited. Not to mention that the available data is further limited because many of these eyes go on to be enucleated based on the histopathologic diagnosis.^{3,5,10,12,13}

That said, a review of the available data suggests that the overall com-

plication rate is between 10 and 20 percent, with vitreous hemorrhage and cataract being the most common complications.^{1,3,5,12,13} Retinal detachment is obviously a concern and was reported in 10 to 15 percent of patients, although follow-up was somewhat limited. Given that these eyes often have significant inflammation, PVR is perhaps the most feared complication, although the exact incidence has not been reported.

In the rare situation that conventional diagnostic and/or treatment measures fail, a vitreoretinal surgeon experienced in this technique may consider FTTCB. Hopefully the considerations discussed here will help you be successful in these challenging situations. **RS**

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New Permanent J-code



ILUVIEN[®]
(fluocinolone acetonide
intravitreal implant) 0.19mg

EFFECTIVE JANUARY 1, 2016

HCP CODE	DESCRIPTION	BILLING UNITS
J7313*	Injection, fluocinolone acetonide intravitreal implant, 0.01 mg	19†

*Follow this guidance when seeking reimbursement: Each ILUVIEN[®] implant is 0.19 mg and must be billed as 19 units using J7313.

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 have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids 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 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

- The most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of >10 mmHg (ILUVIEN 34%; sham 10%).

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

1. ILUVIEN[®] [package insert]. Alpharetta, GA: Alimera Sciences, Inc.; 2014.

*The coding information presented here should not be construed as legal advice, a guarantee of payment or specific guidance on how to code, bill or charge for any product or service. Providers should use their clinical judgment when selecting codes and should use the codes that most accurately represent the product or services delivered.

ILUVIEN[®]
(fluocinolone acetonide
intravitreal implant) 0.19mg

Learn more at ILUVIEN.com

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%)

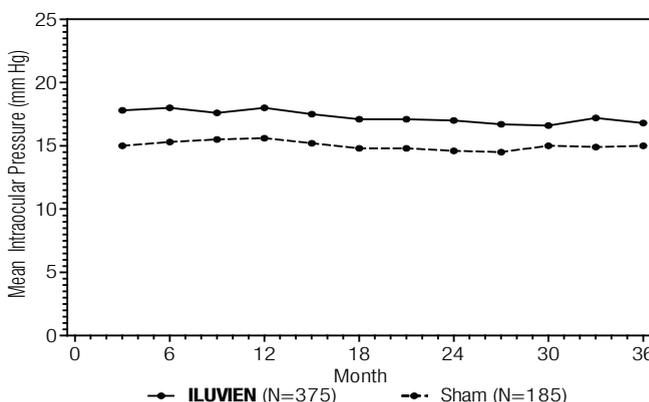


Figure 1: Mean IOP during the study

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
SCIENTES

HORV:

A RARE BUT DEVASTATING COMPLICATION OF ENDOPHTHALMITIS PROPHYLAXIS

Hemorrhagic occlusive retinal vasculitis has been associated with routine intracameral vancomycin use.

By Andre J. Witkin, MD

Ophthalmologists have widely embraced prophylactic intracameral vancomycin during routine cataract surgery to reduce the risk of postoperative endophthalmitis, with excellent results, but this practice has not been without controversy and debate. A large, retrospective study suggested that prophylactic intracameral vancomycin did not reduce the incidence of endophthalmitis.¹ Other authors have suggested that routine prophylactic use may increase the risk of medication toxicity and drug contamination, and promote vancomycin resistance.¹⁻⁴ The Centers for Disease Control & Prevention specifically recommended avoiding vancomycin for routine prophylactic use in surgery to prevent the spread of vancomycin resistance.⁴

More recently, a rare but devastating complication has been associated with prophylactic intraocular vancomycin use in cataract surgery, although the cause of the disease is not definitively known.⁵ My colleagues and I published a series of 11 eyes of six patients who all had a similar appearance of retinal vascular occlusion and hemorrhage with subsequent severe vision loss in many cases, which we termed hemorrhagic occlusive retinal vasculitis (HORV). The following is a case of a woman who experienced severe vision loss and neovascular glaucoma after cataract surgery, along with a review of

the literature. A sidebar summarizes recommendations to avoid HORV (page 29).

Admission After Intracameral Vancomycin

In the summer of 2014, a 66-year-old woman had sequential and uneventful cataract surgery at an ambulatory surgery center, first in the right eye and one week later in the left. In addition to preservative-free lidocaine and viscoelastic, prophylactic intracameral vancomycin (1 mg/0.1 ml) was used during both surgeries. On postoperative day one, the uncorrected visual acuity was 20/25 in each

eye and the patient was happy.

However, 10 days after surgery she first noticed blurred vision in the right eye. The cataract surgeon noted diffuse retinal hemorrhages in the right eye. She was referred to an

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Disclosures: Dr. Witkin has no financial relationships to disclose.

outside retina specialist.

The retina specialist initiated oral valacyclovir 1,000 mg t.i.d. for presumed acute retinal necrosis. One week later, the patient noticed loss of vision in the left eye, as the right eye continued to deteriorate. Similar retinal findings were seen in the left eye, and the patient was referred to our service at the New England Eye Center of Tufts Medical Center.

On presentation to the clinic 18 days after the initial surgery, visual acuity was counting fingers in the right eye and 20/60 in the left. Mild cell and fibrin were noted in the anterior chamber with rare vitreous cell in both eyes. Intraocular pressure was 24 mmHg in both eyes. Most strikingly, the retinal examination showed diffuse microvascular occlusion and extensive intraretinal hemorrhages in both eyes, worse in the right eye than the left (*Figure 1*).

Fluorescein angiography showed stark nonperfusion at the border of active vasculitis (*Figure 2*). The patient was admitted for further evaluation.

Inpatient Treatment

Inpatient treatment included intravitreal ganciclovir and foscarnet bilaterally, high-dose intravenous corticosteroids and oral valacyclovir for the possibility of acute retinal ne-

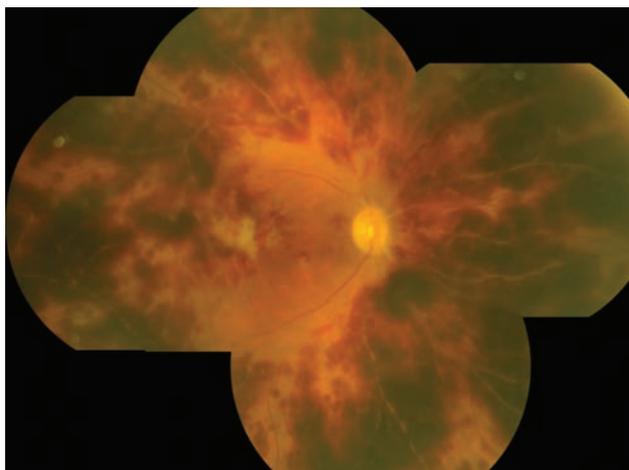
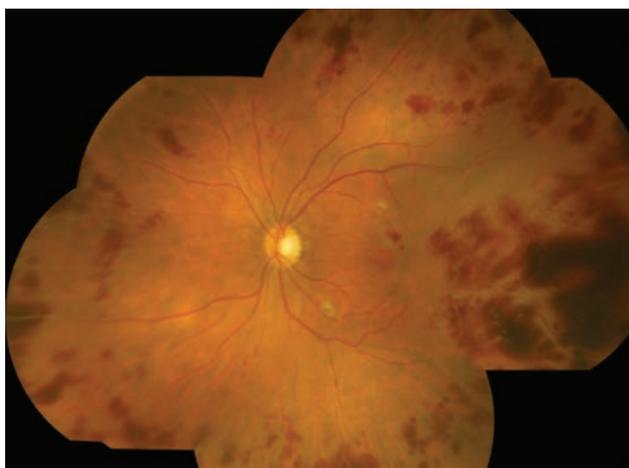


Figure 1. The patient's right eye (above) 18 days after cataract surgery showed diffuse microvascular occlusion and extensive intraretinal hemorrhages worse than the left eye (below), imaged 11 days after surgery.



crosis. Extensive ocular and systemic testing for hematologic, rheumatologic, infectious and neoplastic causes was negative. After 10 days, she was discharged on oral prednisone and valacyclovir, which we tapered over two months. One month after stopping oral prednisone, hypersensitivity skin testing was negative for reactions to vancomycin, sodium hy-

aluronate or lidocaine.

Three months after she first came to our clinic, the patient had developed neovascular glaucoma in the right eye. Despite intravitreal bevacizumab (Avastin, Genentech) injections, visual acuity in the right eye deteriorated to no light perception. She underwent a trans-scleral cyclophotocoagulation to control intraocular pressure. The left eye remained unchanged, with a resultant visual acuity of 20/200 at one-year follow-up. She received intravitreal ranibizumab (Lucentis, Genentech) and prophylactic panretinal photocoagulation in the left eye to prevent neovascular glaucoma.

Identifying Similar Cases

Around the same time as the patient described above was admitted, Laura Nicholson, MD, and colleagues at Massachusetts Eye and Ear Infirmary in Boston published a report demonstrating an identical disease in two other patients.⁶ After we discussed these cases with the authors of that report and other colleagues, a total of 11 eyes of six patients were collected with an identical appearance to our case, and the authors termed the condition HORV.

All 11 eyes had the following characteristics in common:

Take-home Point

Intracameral vancomycin during routine cataract surgery has gained acceptance as prophylaxis against postoperative endophthalmitis. Despite overall excellent results with this approach, a rare but visually devastating complication, hemorrhagic occlusive retinal vasculitis (HORV), has been reported. This article discusses a series of 11 eyes and offers recommendations for preventing and managing HORV.

- Occurrence after otherwise uncomplicated cataract surgery.
- Use of prophylactic intraocular vancomycin during surgery.
- Delayed onset of painless visual loss between one and 14 days after surgery.
- Retinal vascular occlusions associated with hemorrhages in non-perfused areas.
- Relatively mild anterior chamber and vitreous inflammation.
- Poor visual results were common, often complicated by neovascular glaucoma.
- Negative extensive intraocular and systemic workups.

The etiology of HORV remains unknown, but it may be related to an immune reaction to intraocular vancomycin; that was the only agent common to all surgeries in this series.

Because the onset of disease was delayed, HORV does not appear to be related to the so-called “red man” syndrome, which is a mast cell-mediated skin reaction that occurs immediately upon injection of intravenous vancomycin and resolves immediately after discontinuation of medication in-

Recommendations to Prevent and Manage Hemorrhagic Occlusive Retinal Vasculitis

Although the precise etiology of hemorrhagic occlusive retinal vasculitis (HORV) remains unproven, the most likely explanation is an immune reaction to intraocular vancomycin. To prevent HORV, we suggest the following:

- Consider avoiding prophylactic intraocular vancomycin during eye surgery.
- Consider waiting at least two weeks before operating on the fellow eye.
- Suspect HORV if a patient describes delayed onset visual loss after eye surgery.
- Delay or avoid fellow eye surgery if HORV presents in the first eye.
- Avoid intraocular adjuvant medications if HORV develops in the first eye.

Management recommendations for HORV are as follows:

- Consider high-dose systemic and topical corticosteroids.
- Consider early anti-VEGF treatment.
- Early panretinal photocoagulation to non-perfused regions.
- Consider systemic antiviral therapy if acute retinal necrosis is suspected.
- Avoid intravitreal vancomycin if possible.
- Consider ocular and systemic workup for masquerade syndromes.

The American Society of Retinal Specialists (ASRS) is collecting information about suspected cases of HORV. If you have encountered a similar case, report the case details to the ASRS Research and Safety in Therapeutics Committee at this link: <http://goo.gl/vst6yR>

fusion.⁷ The reaction in HORV rather appears more similar to rare reports of leukocytoclastic vasculitis and Henoch-Schönlein purpura secondary to vancomycin, both of which are mediated by antibody/antigen complex deposition causing small-vessel vasculitis occurring

one to two weeks after initiation of intravenous vancomycin.⁸⁻¹⁰

Not Drug Toxicity

HORV likely does not represent a toxic reaction; onset was delayed up to 14 days after surgery, and some of the patients developed the same condition in the fellow eye even when the second cataract surgery was delayed by months or years. In addition, other eyes operated on the same day as those that developed HORV did not have any similar complications despite being operated on by the same cataract surgeon using the same technique, including intracameral vancomycin from the same batch.

If HORV is due to an immune reaction to vancomycin, it is likely extremely rare. In this series, all 11 eyes received intraocular vancomycin at the dose 1 mg/0.1 ml, which has been given intravitreally for

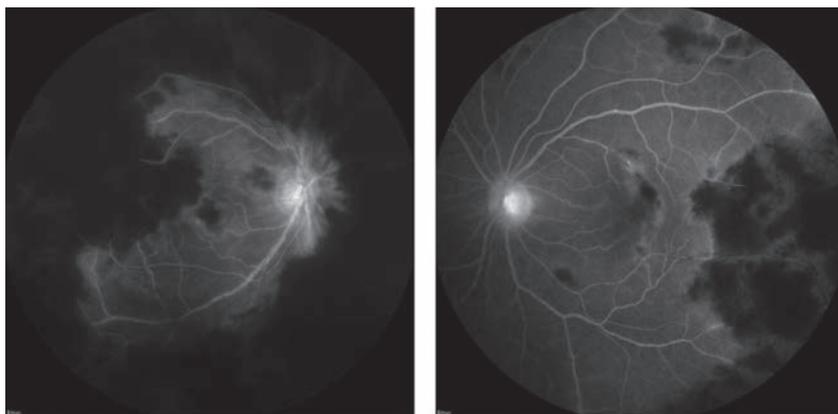


Figure 2. Fluorescein angiogram of the right (left) and left eyes demonstrates complete occlusion of retinal blood flow in regions of retinal hemorrhages as well as leakage from retinal venules and the optic nerve.

many years for treatment of endophthalmitis without a known toxic reaction to the medication. In addition, since the European Society of Cataract and Refractive Surgeons report in 2007,¹¹ tens of thousands of eyes have received intracameral vancomycin after cataract surgery, without emergence of an epidemic of HORV. However, it is possible that there may be some cases of HORV that are less severe and have not been detected or reported. A recent case report demonstrated a milder case of HORV that spontaneously resolved without visual sequelae.¹²

A Poor Prognosis

The natural history of HORV can be visually devastating, because it carries a high risk of neovascular glaucoma. In the cases we discuss here, final visual acuity was 20/100 or worse in eight of 11 eyes. Seven

of 11 eyes developed neovascular glaucoma; four of these eyes had visual outcomes of NLP vision. The outcomes of HORV are particularly disturbing in patients with poor visual outcomes in both eyes due to bilateral HORV.

All patients in this series received high-dose systemic and topical steroids, which may help slow the progression of the disease. Intravitreal anti-VEGF therapy and PRP seemed to delay or prevent the onset of neovascular glaucoma in the eyes with better outcomes. Of note, four eyes in this series received intravitreal vancomycin (and ceftazidime) for treatment of possible bacterial endophthalmitis; these eyes seemed to have particularly poor outcomes, suggesting that the immune reaction may have progressed further after introduction of a second dose of intraocular vancomycin. 

How Intracameral Vancomycin Prophylaxis Emerged

In 2007, the European Society of Cataract and Refractive Surgeons (ESCRS) published results from a large prospective, randomized, multicenter study demonstrating that prophylactic intracameral cefuroxime injection (1 mg/0.1 ml) given at the end of cataract surgery reduced the risk of postoperative endophthalmitis fivefold.¹¹

Since that report, many ophthalmic surgeons have advocated routine use of intracameral antibiotics during cataract surgery.¹³⁻¹⁵ Both the 2011 American Academy of Ophthalmology Cataract Preferred Practice Pattern Guidelines and a 2011 American Society of Cataract and Refractive Surgeons cataract clinical committee review of endophthalmitis prevention noted that the evidence supporting direct intracameral injection was stronger than for any other method of antibiotic prophylaxis.^{15,16}

The percentage of cataract surgeons using prophylactic intracameral antibiotics routinely during cataract surgery more than doubled from 15 percent in 2007 to 36 percent in 2014.¹³ In this country, surgeons have mostly used off-label moxifloxacin or vancomycin, usually mixed by the operating room staff the day of surgery, because the commercial formulation of intraocular cefuroxime used in the ESCRS study is not available in the United States.¹³

Many studies have supported the safety of these off-label medications for intracameral use.^{1,17,18} A recent study, although retrospective, reported a reduction in endophthalmitis rates with prophylactic intracameral vancomycin during cataract surgery with no cases of medication toxicity in almost 10,000 eyes.¹⁸ 

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HOW WILL DRCR.NET PROTOCOL S CHANGE OUR PRACTICE?

Giving us clarity on the use of PRP and anti-VEGF in high-risk PDR.

By Calvin E. Mein, MD

The Diabetic Retinopathy Clinical Research Network (DRCR.net) recently published the two-year results of Protocol S¹ that compared panretinal photocoagulation and intravitreal ranibizumab (Lucentis, Genentech) for patients with high-risk proliferative diabetic retinopathy. Protocol S was designed as a noninferiority study to determine if intravitreal ranibizumab was noninferior to PRP for treatment of high-risk PDR. The study authors concluded that treatment with intravitreal ranibizumab resulted in visual acuity that was noninferior to PRP at two years.

PRP Comes at a Price

PRP has been the mainstay for treatment of PDR since the Diabetic Retinopathy Study Research Group reported its results in the 1970s.² Those of us who have been in practice for more than two decades have had many patients with PDR who received PRP, resulting in stabilization of vision and retinopathy for years without further treatment.

However, PRP comes at a price. Side effects include loss of peripheral vision, development of diabetic macular edema and difficulty with night vision, especially if the patient receives the recommended 2,000–3,000 burns. Should we now consider using pharmacotherapy with anti-VEGF injections instead

of PRP for the treatment of PDR?

As we have moved to treatment to inhibit vascular endothelial growth factor and away from focal/grid laser for DME based on DRCR.net Protocol I, we have noticed a reduction in the progression of nonproliferative diabetic retinopathy to PDR. Thus, the DRCR.net set its primary endpoint accordingly.

Protocol S Design

Protocol S randomized eyes to receive one to three sessions of PRP treatment (203 eyes) or ranibizumab 0.5 mg intravitreal injection at baseline and then every four weeks (191 eyes). A structured retreatment protocol determined repeat injections based on optical coherence tomography and clinical

findings. Eyes with DME received ranibizumab in both groups.

After two years of follow-up, the ranibizumab group improved 2.8 letters while the PRP group improved by only 0.2 letters. With a *P* value of 0.001, the results showed that ranibizumab as given in this study was not inferior to PRP.

Visual acuity was better under the

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Disclosures: Dr. Mein has equity in Regeneron, is a DRCR.net investigator and receives research funding from Alcon, Allergan and Ionic.



Proliferative diabetic retinopathy (left) can have a debilitating affect on vision, but the Diabetic Retinopathy Clinical Research Network Protocol S reports that in select patients, especially those with combined PDR and diabetic macular edema, treatment of PDR with anti-VEGF therapy is noninferior to panretinal photocoagulation and may provide distinct advantages such as better visual acuity, reduced loss of visual field and better night vision.

curve for the ranibizumab group for the entire two-year study period. Visual field sensitivity loss was worse in the PRP group. Vitrectomy was more frequent in the PRP group (15 percent) than the ranibizumab group (4 percent), as was the development of DME.

Clinical Implications

As a practicing ophthalmologist seeing patients with high-risk PDR, how will the results of Protocol S change my approach? When a new patient presents with PDR, several key factors need to be addressed.

The most important is patient compliance and reliability. For me to consider anti-VEGF therapy as the primary treatment, I must be

assured that the patient will return for follow-up and more injections. I do not want to give the patient one injection only to have her or him return some months later with severe progression of PDR when a PRP would have stabilized the condition.

If DME were present along with high-risk PDR, I would lean toward anti-VEGF therapy because it would treat both the DME and the PDR. Anti-VEGF treatments are expensive and ongoing, so I would consider the patient's financial situation. If the patient seems reliable and compliant, I would try anti-VEGF. If the patient were potentially non-compliant, I would use PRP.

Perhaps the best approach would be a hybrid approach of anti-VEGF initially for three injections followed by PRP for more long-term stability. This approach would require a lighter amount of PRP, thus reducing the adverse effects on peripheral vision and development of DME.

Many of my patients who have had full PRP still manifest neovascularization elsewhere (NVE) on widefield fluorescein angiogra-

phy. These patients are ideal for anti-VEGF therapy.

DRCR.net Protocol S has given us a new treatment paradigm for high-risk PDR without the side effects of PRP. For eyes with high risk-PDR and DME, anti-VEGF therapy seems to be the treatment of choice. For eyes with high risk-PDR without DME, a combination of PRP for stability and anti-VEGF therapy to prevent DME would be a good choice. For eyes that have had extensive PRP and still have active NVE, anti-VEGF should be considered.

These clinical situations have no exact answers, and as practicing retina specialists we will have some very exciting discussions about the best approach for high-risk PDR now that DRCR.net has given us the Protocol S results. I look forward to the five-year results of this important ongoing clinical trial. [®]

Take-home Point

The Diabetic Retinopathy Clinical Research Network Protocol S has given us a new approach to high-risk proliferative diabetic retinopathy. While panretinal photocoagulation remains the primary treatment for PDR in many patients, anti-VEGF therapy should be an option for patients who are reliable and present with PDR and diabetic macular edema.

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VITRECTOMY PLATFORMS GO TO THE NEXT LEVEL

EVA has raised the bar on cut rate and vacuum and flow vitrectomy modes, but others have made upgrades, too.

By Gaurav K. Shah, MD, and Vincent Y. Ho, MD

The Enhancing Visual Acuity (EVA, DORC) vitrectomy system has been designed with the highest cut rate available and utilizes an enhanced fluidics system for vacuum or flow vitrectomy modes. Here, we report on our experience with the EVA system in the surgical suite and evaluate its performance based on previous systems we have worked with. In accompanying sidebars, other retina specialists share their experiences with the other vitrectomy systems.

EVA features customizable settings, an intuitive touch screen and programmable foot switches for both vitrector and laser pedals.

Two-Dimensional Cutting

EVA utilizes two-dimensional cutting (TDC) in the 23-, 25- and 27-gauge platforms (20-gauge is avail-

able without TDC), cutting in a forward and backward motion to produce 16,000 cuts per minute (cpm) (*Figure 1, page 35*). While other vitrectomy systems allow surgeons to adjust duty-cycle for port-biased open (core vitrectomy mode) and port-biased closed positions (proportional vacuum/shave mode), the EVA TDC cutters produce a constant duty cycle of 92 percent biased-open position and maintain aspiration even when the blade is in the “closed” position.

The enlarged inner tube aperture of the cutter permits a steady flow rate independent of cutting speed without vacuum buildup in the tubing (*Figure 2, page 37*). This means minimal surge turbulence at the port



View the Videos

6 available online; see custom links throughout the article

Take-home Point

This review of the Enhancing Visual Acuity (EVA, DORC) vitrectomy system evaluates the performance of the device in the surgical suite. The authors find that the 16,000-cuts per minute rate and the fluidics system that combines aspects of traditional venturi- and peristaltic pump-based systems allow for efficient tissue removal in vacuum or flow modes. They also note that the LED illumination provides excellent visualization, that modes and functions are fully programmable to physician preferences and that a broad range of instrumentation at various gauges are available.

ABOUT THE AUTHORS



Dr. Shah is a vitreoretinal specialist and fellowship co-director at The Retina Institute, St. Louis.



Dr. Ho is a surgical vitreoretinal fellow at The Retina Institute. He will be joining New Jersey Retina upon completion of his fellowship.

DISCLOSURES: Dr. Shah is a consultant for DORC and was the first vitreoretinal surgeon in the United States to obtain an EVA system. Dr. Ho has no financial disclosures.

Constellation: All Functions Integrated

By R. Ross Lakhanpal, MD, FACS

The Alcon Constellation vitrectomy system represents a significant upgrade over the previous-generation ACCURUS. I've had the Constellation for about four years now. One of the features I like best about is how it integrates all vitrectomy functions. Here, I share my experience with the Constellation.

Recent Upgrades: The Constellation has a dual-pneumatic cutter with both opening and closing mechanisms instead of the old-style cutter with pneumatic and spring mechanisms.

Cut Rate: The Ultravit vitrectomy probes can achieve up to 7,500 cuts per minute (cpm) in the 23-, 25- and 27-gauge probes. That's basically triple the maximum cut rate of the ACCURUS. You can also control the duty cycle of the probe with the foot pedal, so there's no need to rely on a surgical tech or assistant for that. It also has a momentary setting that is helpful when you're dealing with retained lens material.

Pump and Fluidics: The Constellation uses a venturi pump system. The dual-pneumatic cutter allows for better control of the cut rates and higher cut rates. You can modify the duty cycle to control flow independent of vacuum and cut rate, and you can select three different duty-cycle options at any given cut rate; port-biased open; 50/50; or port-biased closed. This represents significant improvements over the ACCURUS in that at 2,500 cpm the port is only open 30 to 40 percent of the cutting time.

Illumination: The Constellation uses a xenon light source. The halogen light source of the Constellation provided limited visibility. The xenon light utilizes a mirror system technology that allows for co-illumination that focuses all lights into the ports without a beam splitter. Bulb life is longer and the improved fiber optics allow for improved illumination even though lumen size is smaller than the older 20-gauge systems. I was initially skeptical that 27-gauge illumination would provide adequate lighting for fine macular peeling or vitreous base dissection, but I have been pleasantly surprised. An ancillary 25-gauge chandelier system enables bimanual surgery.

Instrumentation: The Constellation has an armamentarium of instruments for all gauges—forceps, picks, scissors, etc. The newer-



The foot switch integrates numerous features.



The user interface has a massive pop-up menu.

generation 25- and 27-gauge instruments are very stiff. The initial 25-gauge instrumentation had some flexibility concerns, but they have been corrected.

Other Features: The interface provides a user-friendly, customizable pop-up menu. It is all on one screen so your surgical technician does not have to scroll through multiple screens to find the settings you need. The machine integrates all your settings—intraocular pressure (IOP) control, gas, fluid-to-air, laser. The first menu shows the types of procedures the surgeon does and you select it. I only do 25- or 27-gauge surgery, so the interface brings up all the settings I prefer. No time is wasted in the setup.

The ACCURUS system utilizes gravity as fluidics control with an IV pole or vented gas-forced infusion to control IOP. In this system, pressure is a static condition. The IOP control of the Constellation automatically adjusts for the infusion tubing and pressure drop when fluid flows through the cannula by measuring and checking the infusion cannula and tubing resistance during priming. The IOP control feature uses a noninvasive flow sensor

that is part of the Constellation cassette and allows it to regulate IOP within ± 2 mmHg throughout surgery, an advantage over using one IOP setting. The surgeon can also control IOP with the foot pedal to control bleeding during surgery.

The foot switch has many integrated features with toggle switches on either side. You can switch to fluid-air exchange, change IOP or duty cycle and go from core to shave mode. The valved cannulas also provide more control in a closed environment. This extra control can be especially important when using profluropropane for detached retina, which does not allow for dispersion of droplets.

C3F8 and SF6 gas tanks are mounted to the system. An "Auto Gas Fill" pack mixes and delivers gas at the desired percentage, allowing you to obtain gas from the machine rather than having an assistant administer it. This can also help control costs; you do not need to deal with different vendors and purchase ancillary supplies.

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and traction on surrounding tissue, particularly during flow vitrectomy mode.

Vacuum Flow Vitrectomy

The VacuFlow Valve Timing intelligence (VTi) fluidics system combines aspects of traditional venturi and peristaltic pump-based systems while overcoming some of their shortcomings to enhance fluidics inside the eye. In traditional venturi-based pumps, the surgeon controls the vacuum and flow follows the vacuum. When a pocket of balanced salt solution is encountered, flow can rapidly increase and lead to iatrogenic retinal breaks because this system depends on the viscosity of the fluid and resistance in the tubing.^{1,2}

On the other hand, traditional peristaltic-based pumps can produce a flow-control system that is independent of fluid viscosity and removes a preset cubic centimeters per minute (cc/min) from the eye, creating a more stable working environment. However, mild flow fluctuations can occur from rotary compression of the flexible tubing.

The VTi aspiration system in EVA combines a series of sensitive computer-controlled operating pistons and closure valves working in small-flow chambers to allow the surgeon to function in vacuum-control or flow-control settings at the touch of a button. In vacuum mode, EVA generates a rise time up to 300 milliseconds and a maximum vacuum of 680 mmHg, both exceeding current vitrectomy systems. This allows for rapid tissue/fluid removal and powerful aspiration.

We have used vacuum mode for the core vitrectomy and maneuvers

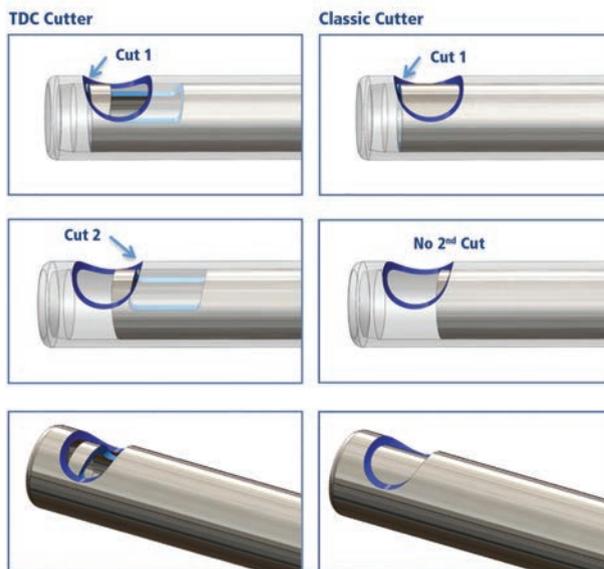


Figure 1. Comparison of the DORC two-dimensional cutter vs. conventional vitreous cutter. Vitreous enters the inner aperture and is cut in a forward and then backward motion, increasing the amount of cutting in a single motion.

like hyaloid or membrane elevation. (*Online Video 1: Vacuum Vitrectomy Mode at <http://goo.gl/yygW9c>*) For retinal detachments, we are still careful when working near mobile retina in vacuum mode, but the 16,000-cpm, 92 percent duty cycle and absence of oscillations associated with standard rotary peristaltic systems increases fluidic stability with less turbulence and without vacuum buildup near the vitrector port.

Using Flow Mode

In flow mode, the surgeon has increased control and predictable fluid/tissue removal at increased aspiration flow rates up to three times faster than other vitrectors at higher cut rates. The surgeon sets the flow rate coming through the port based on cc/min, and the machine automatically adapts parameters such as vacuum and infusion to maintain consistent flow regardless of whether you are in vitreous, fluid or air. (*Online Video 2: Flow Vitrectomy Mode at <http://goo.gl/HpVzeT>*)

In our experience, we created preset, programmed flow vitrectomy settings for 10, 6, 3 or 1 cc/min and cycle through these settings (with the touch screen or foot pedal). The flow setting of 10 cc/min can still efficiently complete hyaloid elevation and core vitrectomy, but improves safety by decreasing peripheral traction and iatrogenic retinal breaks. We mainly use 10-cc/min flow as the workhorse for peripheral shaving, cutting over mobile retina or removing tissue directly over the retina. For even greater control, we will use flow settings of 6, 3 or even 1 cc/min where we can nearly touch the retina while removing vitreous.

EVA also uses vented gas-forced infusion through Automatic Infusion Compensation (AIC) to create a stable surgical environment. At a specified intraocular pressure, the AIC progressively elevates the pressure settings as the aspiration of the vitrector increases. During high-vacuum vitrectomy, the AIC generates a bottle pressure above the set point so the volume of fluid removed from the eye will not exceed the volume of fluid flowing into the eye. Once aspiration ends, the bottle pressure automatically lowers the IOP back to the set point.

AIC prevents eye wall collapse and is adjustable on the touchscreen or foot pedal. For patients with low ocular perfusion pressure, we will decrease the upper limit of AIC control until pulsations of the central retinal artery resolve. Flow can also be enhanced via optional large lumen, high-flow infusion lines attached to DORC cannulas after the valve is manually removed. We mainly use high-flow infusion lines during

Recent Upgrades Boost Stellaris PC Platform

By Kevin J. Blinder, MD

The Stellaris PC phacoemulsification/vitreotomy platform from Bausch + Lomb recently underwent a few upgrades. Some of these modifications include the user interface, valved trocar-cannula entry-site alignment with modified infusion cannula, an integrated laser with wireless foot pedal and a soon-to-be released hypersonic vitrector. I'll explain these and other features of the Stellaris PC.

Recent Upgrades: In my experience, the Stellaris PC user interface seems to be simple to use and logically displayed. The central dial includes all the different functions and it is easy for the scrub tech to control and change settings. The controls are also fully programmable into the foot pedal so the you can change settings without disturbing the scrub tech or assistant.

The valved trocar-cannula entry site alignment includes transparent, valved cannulas for the 23- and 25-gauge systems. The advantage of transparent valved cannulas is that you can see them retro-illuminate under the microscope illumination with the light pipe or chandelier in place, negating the need to turn on the microscope light and allowing for easier instrument exchange under dim lighting. The titanium material of the cannula has a textured feature that improves its use for wound retention. The infusion cannula has a modified tapered design that allows it to accommodate higher flow while providing for a more secure connection to the cannula.

The new fully upgradeable laser module is a standard 532-nm laser that fits seamlessly into the Stellaris PC frame. The foot pedal has also been upgraded to include a safety cover for the laser firing mechanism (avoiding accidental laser activation) and dual-linear control of the laser parameters. The wireless technology allows for less clutter during the case.

Cut Rate: The maximum cut-rate of the Stellaris PC is 5,000 cuts per minute (cpm). The duty cycle adjusts itself as you increase the cut rate, never going below 50 percent, thus maintaining high efficiency. The cutter has a shave mode for vitreous base trimming of mobile, detached retina, and a single-cut mode that allows you to have absolute control when dissecting retinal membranes.

Pump and Fluidics: The Venturi-based pump action, based on vacuum flow, works well in the high-shave cut mode when doing a vitreous base dissection. The core settings can be used to perform vitrectomy with a lower cut rate.

The Stellaris valved cannula.



Illumination: The Stellaris PC has two light sources: xenon and mercury vapor. The latter, with a lower aphakic hazard profile, is suitable for longer cases with decreased risk of the prolonged light exposure leading to phototoxicity. I use the xenon light most often with three filters available to decrease the risk of phototoxicity: a green filter for membrane peeling; yellow for vitrectomy; and amber for air-fluid exchanges. B+L also recently introduced a chandelier system for the 23- and 25-gauge tools.

Instrumentation: Stellaris PC accommodates instrumentation ranging from 23- to 25-gauge, with a 27-gauge to come soon. The newer 25-gauge instruments have improved rigidity, allowing for a wider range of cases. The 23-gauge fragmentation probe is a nice addition, allowing for better fluidics control. This reduces the possibility of the fragmentation aspiration out pacing the infusion, which would often occur when using a 20-gauge fragmentation needle in a 23- or 25-gauge setting. The dual-linear foot pedal allows you



The central dial includes all functions.

to control the fragmentation power along with the aspiration—a helpful feature for retained lens cases.

Other features: The soon-to-be released Hypersonic Vitrector hypersonic liquefaction function is an innovative way of efficiently removing vitreous. The new hand piece will attach to the Stellaris PC with a simple program upgrade. This could potentially change the way we think of vitrectomy and make cut rates and duty cycles obsolete.

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Disclosure: Dr. Blinder is a consultant to Bausch + Lomb, Synergetics and DORC.

27-gauge surgery because flow is directly proportional to radius to the fourth power (Poiseuille's Law) and the opening of a standard 27-gauge infusion line is small.

LED Illumination

EVA uses light-emitting diodes (LED) LEDStar Illumination, which provides up to 40 lumens without degradation of light output. LED bulbs can last more than 10,000 hours vs. about 400 hours for xenon bulbs. The high-intensity LED illumination is particularly advantageous with smaller-gauge vitrectomy because it compensates for reduced transmission through smaller probes. It is safe without ultraviolet or infrared toxicity, and the system includes integrated 435- and 680-nm filters.

EVA includes three separate LED light ports to accommodate use of chandelier lighting systems. Also, light probes are available in four configurations—shielded vs. unshielded and focal vs. diffuse—and include a clear scleral depressor adapter that allows the surgeon to perform external, trans-scleral illumination and simultaneous depression for peripheral shaving. This maneuver is simple and safe but visualization can be decreased in heavily pigmented eyes.

MVR Style One-Step Cannula

The updated one-step cannula system features a microvitreoretinal stiletto-style blade that requires less piercing force upon entry than previous trocar-cannulas (Figure 3). The slit incision allows for sutureless vitrectomy with small-gauge surgery. The translucent, removable valved cannulas provide enhanced visibility when inserting instruments and maintain a closed surgical globe with constant IOP.

A broad range of small-gauge ancil-

Aspiration 27G Vitrectome @ max mmHg

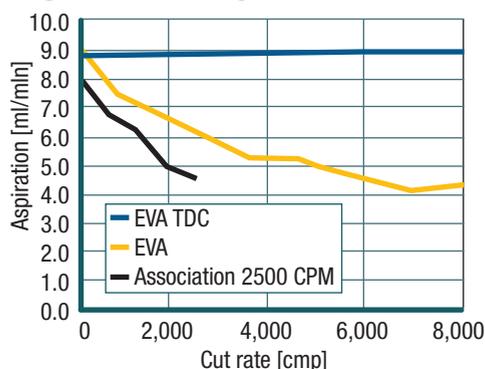


Figure 2. Aspiration flow rates at varying cut rates for 27-gauge TDC vitrectors (basic salt solution at vacuum rate of 550 mmHg). DORC small-gauge TDC cutters maintain constant flow rates independent of cuts per minute.

lary instrumentation is available, including small-gauge peeling forceps. For membrane peels, we often use a hybrid cannula system consisting of a 27-gauge infusion port and cannula for the nondominant hand, 23-gauge cannula for the dominant hand and 27-gauge, two-dimensional cutting vitrector. (*Online Video 3: Hybrid Membrane Peel at <http://goo.gl/iZixQt>*) This allows us to use 23-gauge forceps with a greater surface area and instrument rigidity for grasping membranes or internal limiting membrane.

Control, Customization

The graphical user interface features a 19-inch touch screen, voice feedback, infrared remote control and five language choices, including English and Spanish. It displays functions on the left side of the screen. We have preset and customized settings, which we can modify and save intraoperatively, such as a scleral depression

mode that lowers the IOP to a desired level.

The dual-linear, wireless vitrectomy pedal includes eight switches and two yaw directions. We use the pedal to toggle through different functions. A wireless laser pedal is also available with power adjustment switches. The 532-nm laser can be integrated into the EVA unit as an option, and adapters make EVA compatible with a wide range of laser probe brands.

Other Features and Techniques

EVA also includes broad instrumentation in different gauges including myopic forceps and back-flush tools with shafts 5 mm longer than other tools. EVA can perform anterior segment phacoemulsification; but for the posterior segment, DORC manufactures a 23-gauge fragmatome.

In many cases, we have found the 23- and even 27-gauge TDC cutters can efficiently remove nuclear and retained cortical lens fragments after complicated cataract surgery. Flow mode allows for controlled purchase of lens fragments floating in the vitreous or on the retina surface. (*Online Videos 4 and 5: 23- and 27-Gauge Vitrectomies for Retained Lens Fragments at <http://goo.gl/ryLkHC> and <http://goo.gl/ZAhPh0>*)

We have also found that transconjunctival removal of

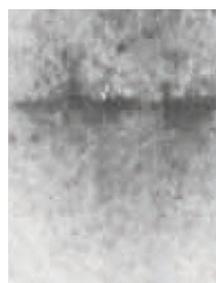


Figure 3. The one-step cannula system produces slit incisions and requires less mean piercing force than previous systems.

silicone oil using the EVA and DORC viscous fluid extraction components to be safe and up to five times more efficient than other systems. The use of flow mode during air fluid exchanges prevents eye wall collapse because a preset cc/min is removed whether aspiration occurs in the fluid or air phase. (Online

Video 6: 23-gauge Transconjunctival Silicone Oil Removal at <http://goo.gl/9PLA42>)

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VersaVit 2.0: Portable, Economical

By Derek Kunimoto, MD

The VersaVit 2.0 vitrectomy system from Synergetics has carved its niche as the small, portable vitrectomy platform. As such, it does not have all the features and options of larger platforms, but it is a versatile unit if your practice demands economy and portability. Here are my impressions of the VersaVit 2.0.

Recent Upgrades: Recent improvements to the VersaVIT 2.0 include the addition of an automated reflux feature, viscous fluid tubing and tips for 23- and 25-gauge silicone oil infusion and extrusion, improved trocars with fewer problems of slippage during surgery and an increase in vacuum pressure to more than 600 mmHg.

Cut Rate: VersaVIT 2.0 provides linear control of cut rate to a maximum cut rate of 6,000 cuts per minute (cpm), adjustable in 500 cpm increments from 2,500–6,000 cpm. Below 2,500 cpm, adjustments to maximum cut rates can be made in increments of 200–600 cpm.

VersaVIT 2.0 allows for three duty-cycle options. The cutter can be biased-open for maximum efficiency during core vitrectomy, neutral (50 percent open/50 percent closed) or biased-closed for maximum safety when working close to the retina.

Pump and Fluidics: A micro-diaphragm pump allows for vacuum

levels above 600 mm Hg. The micro-diaphragm reacts quickly to the surgeon's foot pedal control when increasing or decreasing vacuum. This provides excellent control over both vacuum and flow.

Illumination: An embedded dual port



VersaVit

light-emitting diode (LED) source provides excellent lighting and filters light at very safe levels. I have never had a case where the illumination was inadequate with the VersaVIT 2.0. The advantage of LED lighting is its longevity, which may even outlast the life of the machine. There is also an option for adding a Photon EX, which is a dual-port xenon-based light source for powering smaller illumination products.



VersaVit procedures packs for 20- and 27-gauge will soon be available.

Instrumentation: A full line of instrumentation is available with the VersaVIT platform. The vitrectomy packs are currently available in 23- and 25-gauge. The 27- and 20-gauge packs are planned for release in the second quarter this year.

The instruments are simple, straightforward and user-friendly. Boot-up time is less than 30 seconds, a nice advantage for setup. I consider the VersaVIT 2.0 as the Apple of vitrectomy platforms, with a sleek and minimal interface. Each button is designed to have a specific and necessary function.

Other Features: VersaVIT 2.0 can handle the most complex retinal detachments to the straightforward macular pucker cases. While it does not have a fragmatome, it does have a bigmouth vitrectomy probe to allow removal of mild to moderate nuclear sclerosis. Nor does it have a built-in laser, but a separate laser module can be added.

However, the VersaVIT 2.0 is the most economical of vitrectomy platforms to acquire, and pack prices are competitive. It also is portable, with a small footprint. This platform is well-suited for those who need to move their vitrectomy unit often or have limited space. 

Dr. Kunimoto practices with Retinal Consultants of Arizona in Phoenix.

NONINFECTIOUS UVEITIS: ENRICHING OUR TOOLBOX

Recent advances in localized therapies provide options to traditional systemic immunosuppression.

By Christopher R. Henry, MD, and Thomas A. Albini, MD

Severe vision loss can occur in 25 to 33 percent of uveitis cases, making it one of the most common causes of preventable blindness in the developing world.^{1,2} Traditional systemic immunosuppressive therapy for posterior segment uveitis, allowing successful control of inflammation at one year, is successful in 60 to 70 percent of cases.¹ With acceptable use of less than 10 mg of oral prednisone daily, these therapies are effective in 40 to 60 percent of cases.^{1,2}

Despite the effectiveness of systemic therapy for non-infectious uveitis, still 10 to 25 percent of patients taking immunomodulatory medications for control of uveitis will discontinue these medications within one year because of side effects.¹ Fortunately, local therapies can assist us in controlling disease and new therapies are continuing to be developed to assist us in this mission. In the past year new data has significantly added to our understanding of local treatment of noninfectious uveitis.

Recent updates on the fluocinolone acetonide intravitreal implant (Retisert, Bausch + Lomb), dexamethasone intravitreal implant (Ozurdex, Allergan) and intravitreal sirolimus (Santen) have provided us with additional data on the relative risks and benefits of these therapeutic options. The 54-month data from the Multicenter Uveitis Steroid Treatment (MUST) trial confirms that the fluocinolone implant works at least as

well as systemic therapy. Additionally, data concerning local injection of sirolimus have shown efficacy and the dexamethasone implant is shown to work well for uveitic cystoid macular edema.

MUST Trial 54-Month Update

The MUST trial is a 23-center, partially masked, randomized controlled trial comparing the safety and efficacy of the fluocinolone implant and systemic therapy with oral corticosteroids and immunosuppressive medications for patients with severe noninfectious intermediate uveitis, posterior uveitis or panuveitis.³ The initial study randomized 255 patients (479 eyes) from 2005-2008 to either the surgical implant (129 patients) or systemic therapy (126 patients).

Twenty-four month follow-up found similar visual acuity outcomes results between the two groups.⁴ Through 24 months, the implant group had superior control of intra-

ocular inflammation, but also had a significantly higher risk of requiring cataract surgery, needing treatment for elevated intraocular pressure and developing glaucoma. The systemic therapy group had higher rates of infections requiring prescriptions.⁴

Three-year cost-effectiveness analysis found that systemic therapy was more cost-effective for patients with bilateral disease, but that both were similarly cost effective in patients with unilateral disease.⁵

ABOUT THE AUTHORS



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Dr. Albini is an associate professor of ophthalmology, vitreoretinal surgeon and uveitis specialist at the Bascom Palmer Eye Institute.

Disclosures: Dr. Albini receives consulting fees from Bausch + Lomb, Allergan and Santen.

The 54-month MUST results give us continued reports on the utility of the fluocinolone acetonide implant.⁶ Best-corrected visual acuity data was available in 101 patients (190 eyes) who received the implant and 96 patients (179 eyes) who received systemic treatment. The study found no statistical difference between the groups, with both groups having a mean improvement of around 0.5 lines of vision.

Visual acuity gains were limited, in part, by the fact that 50 percent of uveitis eyes had a baseline vision of 20/40 or better. Among patients with worse than 20/40 vision, visual acuity results were also similar between the two groups, as was visual field sensitivity—with the exception of those in the lower quartile for mean deviation, where the implant group fared worse.

Like the 24-week results, the implant group had a statistically significant improvement in inflammatory control compared to the systemic group through 54 months. Vitreous cells and haze improved in both groups over time, but the implant group had a higher likelihood of having a vitreous haze score of zero and had a greater improvement in the degree of vitreous cells.

The proportion of patients with macular edema was not statistically different between the two groups at 54 months compared to baseline, although macular edema improved more quickly in the implant group based on six-month follow-up data. Despite the expected three-year du-

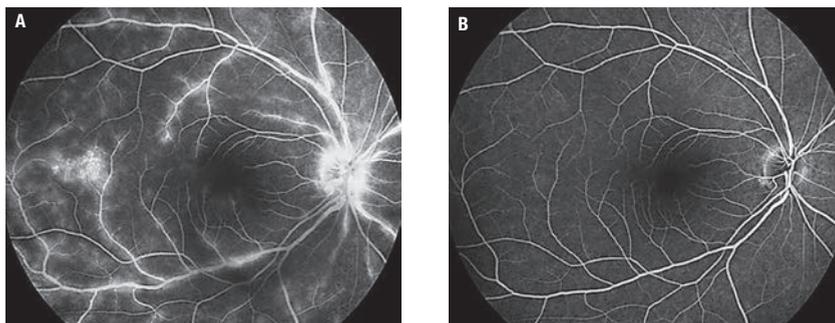


Figure. A 55-year-old woman was treated for intermediate uveitis and retinal vasculitis with mycophenolate mofetil and oral prednisone. Upon attempted taper of oral prednisone, the patient developed recurrent retinal vasculitis (A). The patient underwent an intravitreal Ozurdex injection. Ten weeks after the Ozurdex injection, the retinal vasculitis was dramatically improved (B).

ration of action of the implant, only 10 percent of the implant group eyes required additional implant exchange over the 54-week follow-up.⁶

Implant Side Effects

A companion study compared the side effects and quality-of-life measures between systemic therapy and the fluocinolone acetonide implant over the 54-week follow up.⁷ This study found that the incidence of elevated IOP, glaucoma, use of IOP-lowering therapy and need for IOP-lowering surgery were all significantly higher in the implant group.

Development of cataract was almost universal in the implant group, with 87.7 percent of eyes having had cataract surgery compared to 43 percent in the systemic group. Systemic side effects were similar between both arms and specifically not higher among the systemic immunosuppression group. Quality-of-life measures

were similar among the two groups.⁷

The companion study authors suggested that systemic therapy may be preferable to the implant in patients with bilateral disease due to superior cost-effectiveness and fewer ocular side effects. Nevertheless, the fluocinolone acetonide implant remains a viable treatment option, particularly in cases of unilateral disease, among those who cannot receive systemic therapy, as well as among those who fail systemic treatment.

Preliminary results of a Phase III trial of a second fluocinolone sustained-release device, the Medidur fluocinolone insert (pSivida Corp.), reported the device met its primary endpoint of prevention of recurrence at six months in the treatment of posterior noninfectious uveitis.⁸ The trial will continue to follow patients for three years, and we will learn more about the rate of local complications of the two implants.

Take-home Point

The development of new intravitreal therapies for non-infectious uveitis is encouraging. Three recent studies have indicated that an increasing number of local treatments are or will soon be available for chronic noninfectious uveitis involving the posterior segment. Whether used as monotherapy or as an adjunct to systemic therapy, these agents will provide the uveitis specialist with increased options, especially for patients who cannot tolerate traditional systemic immunosuppression or want to avoid it.

Dexamethasone for Uveitic CME

Rahul Khurana, MD, reported on one-year results of the TAHOE (prospective evaluation of susTained-release dexAmethasone intravitreal implant fOr uveitis macular Edema) study at the Retina Society 2015

meeting in Paris.⁹ The TAHOE study is a prospective, noncomparative, interventional trial assessing the effectiveness of a 0.7-mg dexamethasone intravitreal implant for treatment of persistent cystoid macular edema in eyes with quiescent uveitis.

Ten patients were treated with the dexamethasone implant. They were monitored monthly and retreated with the implant after day 90 days if any recurrent CME was noted on optical coherence tomography. Average presenting findings were: visual acuity, 20/63; and central subfield macular thickness, 481 μm . At three-month follow-up, average vision improvement was 14 letters ($p=0.0001$). At 12 months, two-thirds of eyes had improved by 3 or more lines of vision.

Over the 12-month follow-up, patients required an average of two dexamethasone injections to control macular edema, although four patients required only a single injection. The mean time to recurrence of CME was 6.3 months. One eye had an IOP rise greater than 25 mmHg, and two of eight phakic eyes had cataract surgery due to cataract progression. Results of this study suggest that the 0.7-mg dexamethasone implant was effective in treating persistent CME in quiescent uveitis eyes, although future comparative trials involving other treatments are needed.

SAKURA Intravitreal Sirolimus Trial

SAKURA (Study Assessing Double-masked Uveitis Treatment) is a multicenter, double-masked randomized trial assessing the safety and efficacy of intravitreal sirolimus for treatment of noninfectious posterior segment uveitis.¹ Sirolimus acts as an mTOR inhibitor that disrupts T-cell proliferation and the release of IL-2 and other inflammatory cytokines.^{10,11}

Phase III results are now available.¹

The study had a monotherapy design in which a 44-ug intravitreal preparation of sirolimus served as an active treatment control group and was evaluated against 440-ug and 880-ug intravitreal sirolimus preparations. The study remained masked through six months, during which patients in each group received injections at baseline, two months and four months.

The primary endpoint was a vitreous haze score of zero at month five in the study eye. To be included in the study, patients were required to have a presenting vitreous haze score of greater than one and 20/400 BCVA or worse in the study eye. Patients ceased immunomodulatory therapy at least 30 days before the first day of the study, and topical corticosteroids were tapered before day one.

The intent-to-treat population included 117 patients in the 44-ug group, 114 in the 440-ug group and 117 in the 880-ug group. At five months, 22.8 percent of patients in the 400-ug group achieved a vitreous haze score of zero compared to 10.3 percent of the 44-ug group ($p=0.025$). In contrast, only 16.4 percent of patients in the 880-ug group achieved a vitreous haze score of zero.

Sixty-nine patients in the series were taking at least 7.5 mg of oral prednisone at baseline and were studied on an intent-to-taper basis. Twenty of 26 patients (76.9 percent) in the 440-ug group were tapered to less than 5 mg/day of oral prednisone without needing rescue therapy compared to 14 of 22 (63 percent) of patients in the 44-ug group, but this result was not statistically significant.

ERM Influence On Central Retinal Thickness

This study also evaluated the change

in central retinal thickness, although it was not a primary or secondary outcome. The greatest improvements in central macular thickness were seen in patients without an epiretinal membrane receiving the 440-ug dose of sirolimus, in whom the reduction was greater than 50 percent, whereas those in the 44-ug group showed a reduction in central macular thickness of less than 5 percent.

In patients with an ERM, the reduction in central macular thickness was similar between the 440-ug and 44-ug-dose groups. Increase in IOP of greater than 35 mmHg persisting more than seven days was seen in only one patient in each the 44-ug and 440-ug groups (0.9 percent of each group) and three patients (2.6 percent) in the 880-ug group. ¹⁵

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The Case for Certified Personnel

Reimbursement and regulatory challenges demand certified staff. By David Gavin, MBA

Reductions in Medicare payments have made it necessary for retina specialists to become more efficient. Meaningful use and quality reporting requirements have burdened physicians with the demands for more documentation to avoid additional Medicare penalties. To maintain practice efficiency and meet these additional documentation requirements, physicians are relying on higher-level certified clinical staff.

Ophthalmology specific certifications include Certified Ophthalmic Assistant (COA), Certified Ophthalmic Technician (COT) and Certified Ophthalmic Medical Technologist (COMT). An employee must complete certain experience and educational requirements and pass a certification test. Certification shows the employee's commitment to the practice and specifically to ophthalmology as a vocation. Additional information on the certification process and requirements can be found on the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) website at JCAHPO.org.

Certification Cost vs. Benefit

Studies have shown that certified personnel increase practice efficiency and quality of care. However, with better-trained employees come higher personnel costs. A cost-benefit analysis can determine if the extra costs outweigh potential Medicare penalties and lower productivity of non-certified staff.

Among the metrics this analysis should measure are: the number



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of additional patients the physician can see with a certified assistant and the additional practice revenue; potential for better documentation and fewer errors; and improvement in patient satisfaction. Other potential benefits include how well certified staff helps the physician manage clinic time.

What It Means in the Clinic

Meaningful use requires that certified personnel use computerized provider order entry for medication, laboratory and image ordering. Without certified personnel, the onus is on the physician to enter that information, thus reducing efficiency and the time a physician can spend with patients.

Failure to properly order medications and testing in the electronic medical record will result in Medicare payment penalties ranging from 1 to 3 percent depending on what stage of meaningful use the practice is in.

Medicare will not only base future payments on efficiency, but also on quality measures. Many physicians use certified employees as scribes to meet meaningful use requirements. A certified employee has proven job knowledge in ophthalmology and

that gives the physician the reassurance that patients will receive the highest quality of care.

Incentives for Certification

Not all clinical employees may want to become certified, so how do you incentivize them to do so? You can simply make it a job requirement and let your employees know they have a certain period of time to obtain their certification. Explain why you are requiring this certification and the benefits for the employee and practice.

For the employee, certification makes her or him more marketable as more physician offices move toward hiring certified personnel. Some retina offices offer incentive programs such as reimbursement for study materials and the exam cost. Other offices offer an immediate pay increase upon successful completion for the certification exam. Or, you can offer some combination of these incentives.

Certified personnel bring an increased job knowledge that has shown to improve physician productivity, efficiency and quality of care while helping the physician meet the ever-increasing pay-for-performance and meaningful use requirements. With more such mandates on the horizon, each practice needs to make sure it has the certified work force to comply. The benefit of having certified personnel can far outweigh the additional costs to the practice. 

Mr. Gavin is practice administrator at Palmetto Retina Center, West Columbia, S.C.



Coding and Reimbursement Updates

Changes in 2016 amount to a sharp reduction in physician reimbursements.

This year brings several coding and reimbursement changes specific to retina specialists. The most notable change affects panretinal photocoagulation. Several changes combined to reduce physician reimbursement for PRP by 66 percent (*Table*). Here, I'll review what those changes are and how they can impact practice reimbursements.

Changes to PRP Code

First, the 2016 *Current Procedural Terminology* (CPT) revised code 67228 representing PRP to read:

*Treatment of extensive or progressive retinopathy (e.g., diabetic retinopathy), photocoagulation.*¹

Before this year, the descriptor for CPT 67228 included the verbiage "one or more sessions." Removing this descriptor facilitates charging for staged PRPs within the global period. Medicare Carrier Palmetto GBA discusses codes defined as "one or more sessions" accordingly:

*These codes should be reported once for the defined global surgery period to include all sessions during that period. For example, when laser photocoagulation of diabetic retinopathy requires four sessions, CPT code 67228 should be reported once. This includes the surgery and appropriate follow-up, post-operative management, over the ensuing 90-day global surgery period.*²

Many retina specialists deliver PRP over more than one session. Historically, when PRP treatment was split over more than one session, payment for the first laser included all laser sessions on the same eye during the 90-day global period. Partly as a response to this change, the Centers

Table: National Medicare Rates For Retinal Detachment Repair Codes

CPT	2015	2016	Change (%)
67107	\$ 1,234.68	\$ 1,031.88	-16%
67108	\$ 1,631.02	\$ 1,315.81	-19%
67113	\$ 1,772.96	\$ 1,430.38	-19%
67228	\$ 1,016.20	\$ 345.15	-66%

for Medicare & Medicaid Services (CMS) reduced the global period for CPT 67228 from 90 days to 10 days, making it a minor procedure. The revised Medicare Physician Fee Schedule released in mid-January reflects the global period update.³

Impact on the Practice

What does this mean to the practice? Now the surgeon may charge for each session of PRP. For example, if 800 laser pulses are delivered in session one and the patient returns three weeks later for a second session of 800 laser pulses in the same eye, both sessions can be reimbursed in full. In another example, when PRP was delivered to the right eye and subsequently delivered to the fellow eye within 90 days, the claims required modifier -79 representing an unrelated service. Now, modifier -79 is not necessary when PRP of the fellow eye is delivered outside the new 10-day global period.

Other Retinal Code Changes

The other two relatively common retinal laser procedures, CPT 67210 (focal laser) and CPT 67145 (prophylaxis for retinal detachment) did not change. They still include the "one or more sessions" designation and retain

90-day global periods.

Significant decreases in reimbursement rates for retinal detachment repair codes 67107, 67108 and 67113 occurred in 2016 as well³ (*Table*). Unfortunately, the reduction (excluding 67228) appears to be part of a two-year phase-in. This means we will likely see further reductions to codes 67107, 67108 and 67113 in 2017.⁴ Reimbursement rates for other common surgical services, such as intravitreal injections (67028) and vitrectomy membrane peels (67041, 67042), had little or no change in 2016.

New Code for Compounded Drugs

CMS released a new supply code for compounded drugs. According to MLN Matters Number MM9846, Health Care Procedure Coding System (HCPCS), code J7999 *Compounded Drug, Not Otherwise Classified* (NOC) is effective January 1, 2016, for compounded drugs.⁵ The Medicare Claims Processing Manual stipulates "beginning in July 2015, claims for compounded drugs shall be submitted using a compounded drug, not otherwise classified (NOC) HCPCS code."⁶

Some Medicare carriers, like
(Continued on page 46)



An App to Monitor Patients At Home

Mobile system can alert retina specialists to vision changes before patients can.

Darius Moshfeghi, MD, knows that patients with macular degeneration or retinal vein occlusion are often loathe to call their doctors if they notice a slight but questionable change in their visual function between appointments, but he's found a way to override that hesitance and provoke a preemptive call to get the patient back into the office before more serious vision loss can occur.

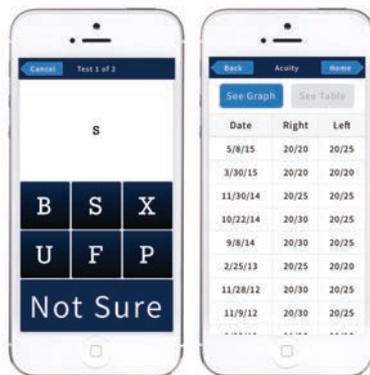
For about two years, Dr. Moshfeghi, a professor of ophthalmology at Stanford University Medical Center, has sent upwards of 100 patients home with the mobile Checkup app from DigiSight Technologies. He has been a beta tester for the app.

How Checkup Works

Between clinic visits, once or twice a week, or more frequently if Dr. Moshfeghi prescribes it, patients take any number of visual function tests using the Checkup on a mobile device in their own home. The app uploads the results to the cloud and sends him or his staff alerts if something untoward registers in the test results.

Checkup is one of three tools that DigiSight now integrates into its Paxos platform launched last year. The other tools include Paxos Scope, a hardware add-on with a mobile application that captures anterior and posterior images of the eye wherever the patient is, and Paxos Analytics, which enables real-time insight on clinical study outcomes with high-frequency longitudinal data not previously available. DigiSight expects to launch Analytics this year.

Tests patients can perform on



The left screen shows the visual acuity test mode on the Checkup app, the right screen the results over time.

Checkup include visual acuity, Amsler grid, low-light acuity, inverse acuity, contrast sensitivity, low light contrast, color discrimination, acuity and contrast, and the DigiGrid proprietary grid test.

'Sense of Security'

Dr. Moshfeghi took time out from his retina specialty clinic to talk about how he's used Checkup to follow patients with retinal disease. "This gives patients a sense of security that their vision is testing around where it was at the clinic, or maybe it's a little up or down, but it doesn't just rely on the patient," he says. "It has its own proprietary algorithm that has preset inflection points that, if the patient's test falls below a certain threshold, it will alert the monitoring physician."

He adds, "Sometimes the patient's vision will drop two lines and it doesn't bother the patient, but the algorithm will notify us."

When following patients with chronic retinal disease, retina specialists make most of their decisions

based on empirical data. "While the patient hasn't had fluid accumulate in the nine weeks before, we'll have the patient follow up in nine weeks—but that doesn't mean fluid can't accumulate before that," he says. "Because I know what kind of patient I'm dealing with—whether the patient has macular degeneration or RVO—and if the fluid does return earlier than expected, I can bring this patient in and see what's going on."

Age Is No Barrier

He has found the app to be suitable for any patient. "If patients are particularly anxious about their vision, I'll put them on the app," he says. "It gives them a lot of reassurance." He has prescribed Checkup for patients as young as 10 years old.

"About 95 percent of the patients I've given it to take to it very easily," Dr. Moshfeghi says. Getting the testing interval right is an important consideration for the clinician. "I first started them all on daily testing, but nobody does daily testing. If you put them on weekly or twice-weekly schedule, particularly for patients who are relatively stable, low-risk patients, they use it all the time," he says.

He adds, "A lot of times when you call patients to follow up on a test, they are unaware the test picked up something, which only reinforces their belief in the system."

Dr. Moshfeghi says of Checkup: "Having test-driven it, I think it's ready for utilization. It can be a value-add to any practice." ^{RS}

Dr. Moshfeghi disclosed he has no financial interest in DigiSight.

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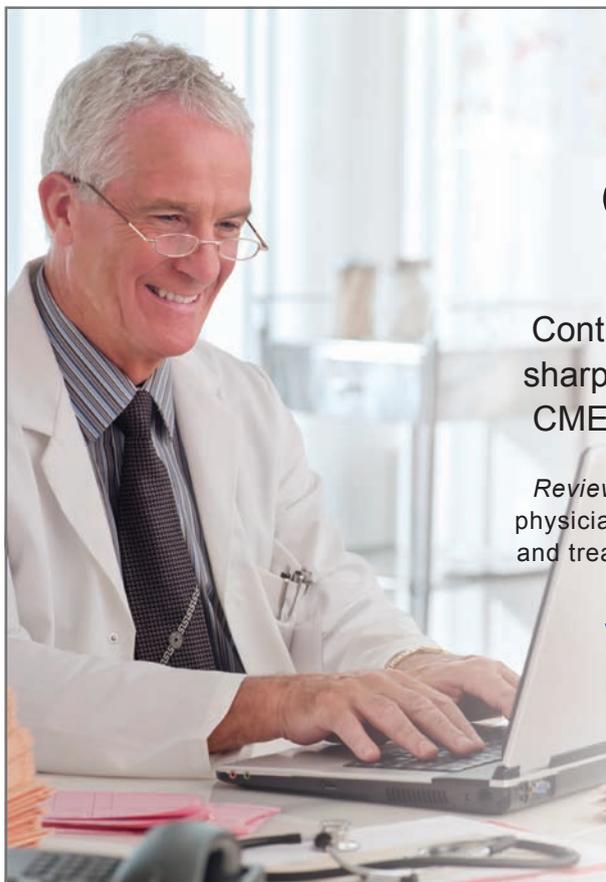
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2016 Coding and Reimbursement Updates

(Continued from page 43)

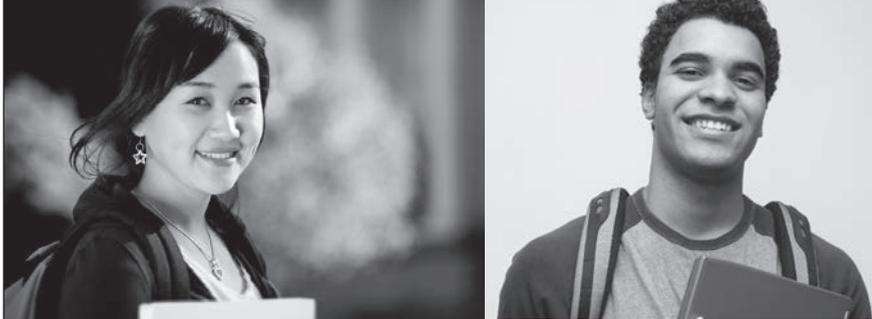
Noridian, mandate the use of J7999 for compounded bevacizumab (Avastin, Genentech).⁷ Some carriers, at the time this article was written, have not yet implemented J7999 for compounded drugs including bevacizumab and may still require other codes. We encourage you to monitor your claims and check the local carrier information for updates.

Other changes occurred in 2016, but none as immediately impactful to retinal surgeons. Continue to monitor your carriers for updates and changes to current policies and Local Coverage Determinations (LCDs).⁸

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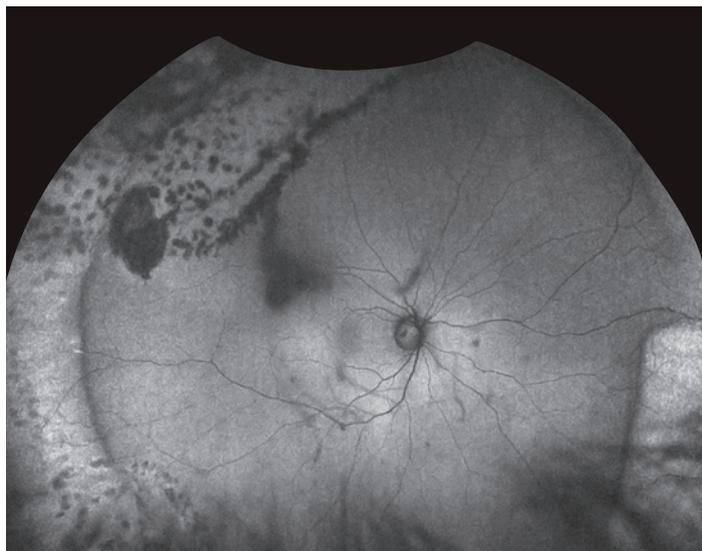
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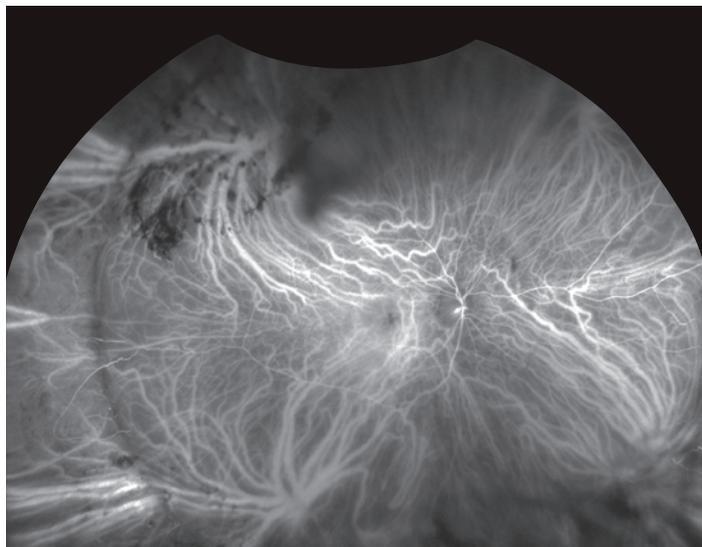
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