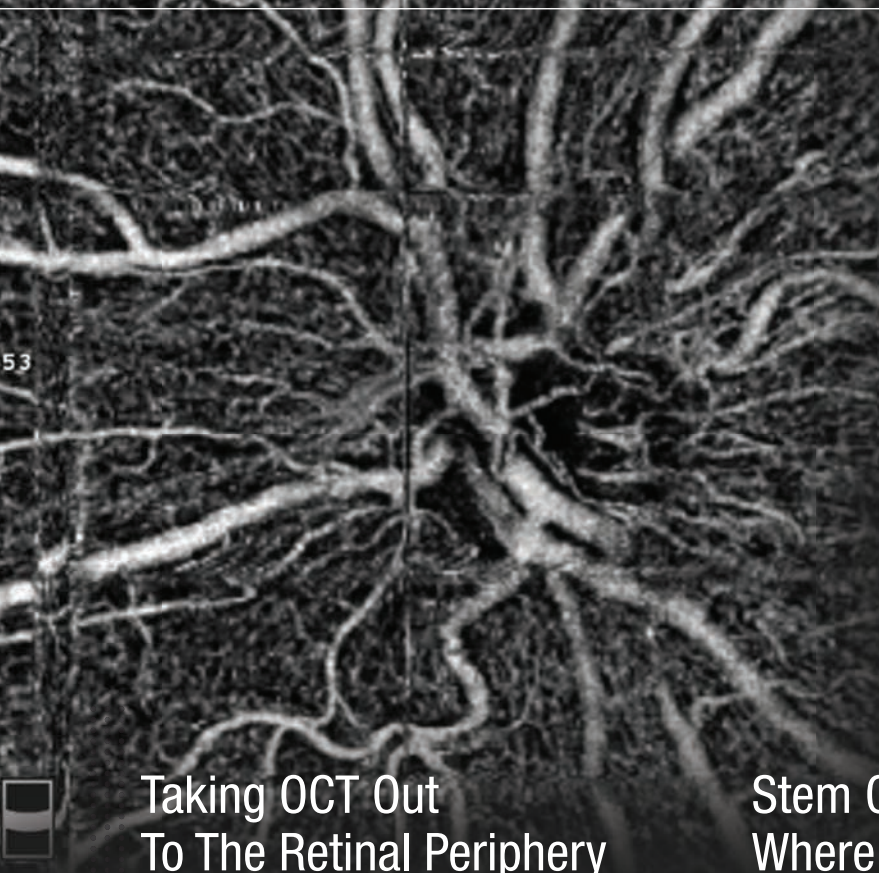
A PUBLICATION BY REVIEW of Ophthalmology

RETINA SPECIALIST

SEPTEMBER 2016



Focus on Imaging

WILL OCT ANGIOGRAPHY REPLACE FA?

A close look at how this modality compares with the gold standard.

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Taking OCT Out To The Retinal Periphery

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Stem Cells for Retina: Where Are We Now?

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Online Video MIVS and Post-op Endophthalmitis

PAGE 44

Online Video A Novel Approach For Surgical PVD

PAGE 20

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

WHEN VISUAL ACUITY STOPS CLIMBING

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

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

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

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

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

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

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

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

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

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

START EARLY

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

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

The OZURDEX® approach:

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

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

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions

Diabetic Macular Edema

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

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

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

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

Retinal Vein Occlusion and Posterior Segment Uveitis

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

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

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

1. OZURDEX® Prescribing Information.

Allergan

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

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

INDICATIONS AND USAGE

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

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

Diabetic Macular Edema

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

CONTRAINDICATIONS

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

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

Retinal Vein Occlusion and Posterior Segment Uveitis

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

Adverse Reactions Reported by Greater than 2% of Patients

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

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

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

Diabetic Macular Edema

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

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

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

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

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

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

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

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

Cataracts and Cataract Surgery

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Risk Summary

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

Animal Data

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

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

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

PATIENT COUNSELING INFORMATION

Steroid-related Effects

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

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

Intravitreal Injection-related Effects

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

When to Seek Physician Advice

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

Driving and Using Machines

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

Rx only

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A PUBLICATION BY REVIEW
RETINA SPECIALIST

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By Charles C. Wykoff, MD, PhD

Retina Specialist's Legion of Honor

Napoleon Bonaparte, the first emperor of France, is one of the most successful and controversial military leaders in human history. He bestowed medals, awards and titles generously to encourage his soldiers and heighten morale, creating the first modern order of merit, the Legion of Honor.

Following Napoleon's lead, I want to praise the exceptionally talented Generals behind *Retina Specialist*. Our standing columns provide targeted insights into the many facets of being a retina specialist. Philip Rosenfeld, MD, PhD, coordinates our "Medical Retina Fellows Forum," providing insights from recent clinical observations and trials. See page 13 for his succinct summary of the active trials moving combination therapy for wet AMD into the clinic.

In "Retina Rounds," Lisa Olmos, MD, delivers a mystery case or management dilemma certain to hone your clinical skills. Paul Hahn, MD, unwraps "Surgical Pearls" with linked videos. Having difficulty lifting the hyaloid? See page 20 for his latest recommendations.

Emmett Cunningham MD, in "Clinical Trial Closeup," explores pertinent clinical trials, this time focusing on suprachoroidal steroid delivery. Kirk Mack helps maximize your coding and avoid audit red flags. Being in the middle of an audit with my group, I can promise you they are painful and incredibly resource-consuming. Let Kirk help keep you on track.

Efrem Mandelcorn, MD, leads the newest addition to our standing columns, "North of the Border," from Toronto, delivering an ex-United States perspective.

This quarterly edition is dedicated to ocular imaging. In "Innovation Insight" on page 51, David Huang, MD, PhD, one of the co-inventors of optical coherence tomography, gives his perspectives on where OCT has been and where it's going. Caroline Baumal, MD, and Talisa de Carlo, MD, describe the virtues of OCT angiography (*page 22*), and Netan Choudhry, MD, modifies his spectral-domain OCT machine to capture peripheral retinal pathologies as you have never seen them (*page 30*).

Walking the halls of the American Academy of Ophthalmology annual meeting reminds me of Napoleon's approach. Some of our colleagues appear to have literally dozens of ribbons and pins dangling from their name tags. It's not easy to get the ribbons on straight with just the right length flapping below. How many ribbons will you be wearing at the AAO?

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

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

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

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

Adverse Reactions

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

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

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

ILUVIEN®
(fluocinolone acetonide intravitreal implant) 0.19mg

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

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

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with **ILUVIEN**, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

Table 1 (continued)

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

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

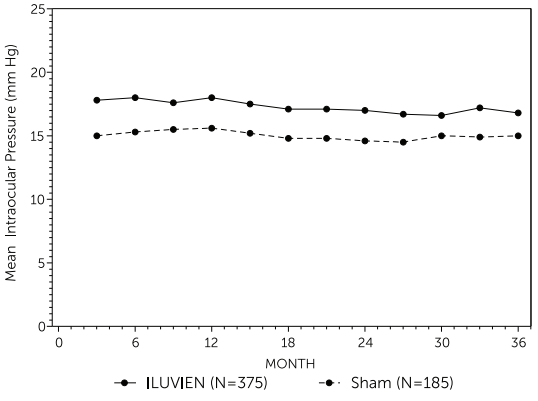
[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

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

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

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

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

USE IN SPECIFIC POPULATIONS

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

Manufactured for:
Alimera Sciences, Inc. • 6120 Windward Parkway
Alpharetta, GA 30005 • Patented.
See: www.alimerasciences.com

1-844-445-8843. Printed in USA. US-ILV-MMM-0335. 6/16

ALIMERA SCIENCES

A PUBLICATION BY REVIEW

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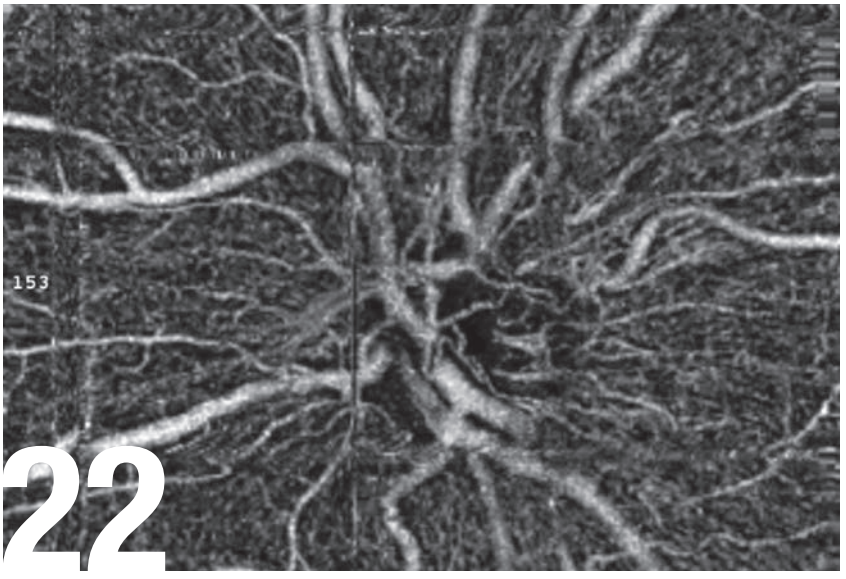

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SEPTEMBER 2016

FEATURES

Focus on Imaging

DEPARTMENTS

IN BRIEF

• **Second Sight Medical Products** announced positive five-year outcomes associated with clinical cases using the **Argus II Retinal Prosthesis System**. Researchers followed 30 subjects implanted with the Argus II in 10 centers in the United States and Europe. Clinical trial results showed that subjects' visual function improved after implantation with the Argus II and that the improvements were sustained over five years. Results also demonstrated that the device had an acceptable safety profile.

• The **California Institute for Regenerative Medicine** will collaborate **with AiVita Biomedical** on development of stem-cell-derived, 3D-transplantable retinas to treat vision loss. AiVita's role is to manufacture the 3D-retinal organoids and use its regulatory expertise. The University of California Irvine will test the product for safety and efficacy in relevant models of retinal degeneration.

• **IBM**, which is forming the Watson Health medical imaging collaborative, named **Topcon** to be one of 16 partners in the collaborative. Topcon and other partners, including academic medical centers, health systems, ambulatory radiology providers and imaging technology companies, will utilize IBM's Watson with medical imaging devices, electronic health records, radiology and pathology reports and other clinical tools. Topcon will leverage its family of imaging devices to facilitate and optimize the Watson training process.

Trials: Anti-VEGF Biosimilars Comparable To Lucentis

Three clinical trials of biosimilars to Lucentis (ranibizumab) moving through the development pipeline have shown comparable safety and efficacy profiles to the index biological agent, investigators reported during the 34th annual meeting of the American Society of Retina Specialists (ASRS) last month.

India has been out in front with anti-VEGF biosimilars, with Intas Pharmaceuticals bringing the first, called Razumab, to market there last year. At ASRS, Srinivas Joshi, MD, of Hubli, India, reported on a trial of 119 eyes of 95 patients who received Razumab injections between November 2015 and May 2016. The patients had neovascular age-related macular degeneration, macular edema secondary to retinal vein occlusion or diabetic retinopathy. "No serious drug-related adverse events were identified," Dr. Joshi said.

Central macular thickness improved from 345.9 ±128.84 µm at baseline to 287.65 ±90.29 µm after 30 days ($p<0.0001$), as did best-corrected visual acuity from 0.59 ±0.43 logMAR to 0.50 ±0.37 logMAR ($p=0.0467$), Dr. Joshi said.

"While the long-term safety and efficacy remain unknown, these short-term results suggest that Razumab could become a safe, low-cost therapy for macular diseases in developing countries," Dr. Joshi said.

Another study from India showed similar results. Alay S. Banker, MD, from Ahmedabad, reported on a longer-term study of a Lucentis biosimilar with a mean follow-up of 13.3 weeks.

Ninety-four eyes of 69 patients received a total of 154 injections. Twenty-six eyes had choroidal neovascularization from AMD, 43 had diabetic macular edema, 13 had macular edema due to RVO and 12 had retinopathy of prematurity that warranted treatment. "All eyes had resolution of retinal edema with central subfield thickness reducing from a mean of 359.65 µm to 298.68 µm ($p<0.01$)," Dr. Banker said. Additionally, mean logMAR visual acuity after injections improved from 0.53 to 0.37 ($p<050$).

None of the patients reported minor side effects like blurred vision, ocular pain, bulbar injection or intraocular inflammation, and none experienced any serious ocular or systemic effects, Dr. Banker said. "This new biosimilar ranibizumab could become a safe, low-cost therapy for retinal disease," he said.

Pfenex, which is developing the biosimilar PF582, reported on the first in-human study of a Lucentis biosimilar in the United States. Hubert C. Chin, MD, chief medical officer, reported at the Ophthalmology Innovation Summit at ASRS that the Phase I/II trial involved 25 patients with wet AMD who had never had anti-VEGF treatment;

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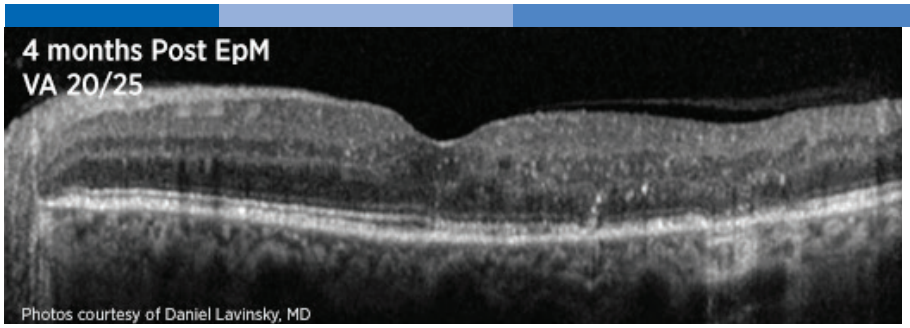

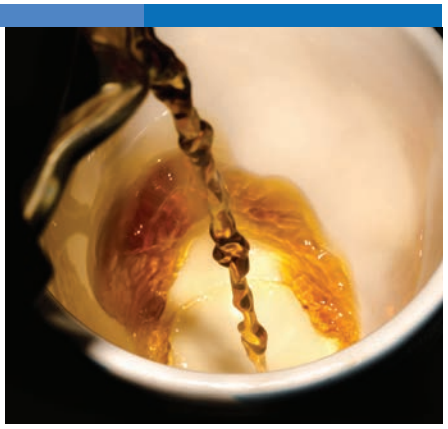

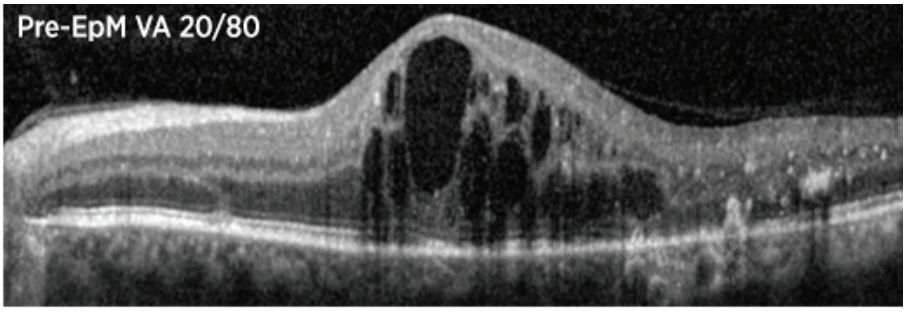

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13 received PF582 and 12 Lucentis injections at three monthly intervals.

The trial reported no meaningful differences in intraocular pressure, systemic adverse events or safety or tolerability findings between the biosimilar and index agent.

Dr. Chin also noted that Pfenex had regained full rights to the agent after Pfizer turned them back. Pfizer acquired the rights when it acquired Hospira last year.

Could Organ Transplant Drug Be New Agent for Uveitis?

Intravitreal injections of the anti-rejection agent sirolimus may be a new treatment option to reduce vitreous haze in patients with noninfectious intermediate and posterior uveitis, according to results from the SAKURA Study 1 reported at ASRS.

Sirolimus inhibits mTOR—or mechanistic target of rapamycin—which regulates cellular metabolism and growth. The Phase III SAKURA Study 1 involved 347 subjects with baseline vitreous haze scores (VH) greater than 1, 118 of whom had a diagnosis of intermediate uveitis. They received three different doses of sirolimus—44 µg (active control), 440 µg or 880 µg—at days one, 60 and 120.

At five months, the proportion of the intermediate uveitis subjects who achieved the primary endpoint, VH 0, was 7 percent for 44 µg, 24.3 percent for 440 µg (p=0.056 vs. 44 µg) and 26.3 percent for 880 µg (p=0.031 vs. 44 µg). In the intermediate uveitis group, the secondary endpoint, VH of 0 or 0.5+, was achieved by 27.9 percent for 44 µg, 54.1 percent for 440 µg (p=0.023 vs. 44 µg) and 57.9 percent for 880 µg (p=0.008 vs. 44 µg). The mean VH improvement at five months was -0.77 for 44 µg, -1.17 for 440 µg (p=0.02 vs. 44 µg) and -1.13 for 880 µg (p=0.037 vs. 44 µg). Response rates were higher in this subgroup than in the overall study population, said investigator Pauline T. Merrill, MD, of Illinois Retina Associates.

Sunil Srivastava, MD, of the Cleveland Clinic, also reported on 12-month results from SAKURA Study 1 of 347 subjects with noninfectious posterior uveitis on the same dosing regimens. At six months, subjects transitioned to an open-label treatment period during which they received injections of 880 µg every two months for the next four months.

At the end of open-label treatment (month 12), the proportion of subjects achieving VH 0 or 0.5+ was 42.1 percent overall (43.9 percent for 440/880 µg, 41.9 percent for 44/880 µg and 40.5 percent for 880/880 µg).

"The greatest visual benefit at month 12 was seen in subjects with worse best-corrected visual acuity at baseline," Dr. Srivastava said.

The 440/880 µg group, patients with baseline BCVA <20/100 had a 9-ETDRS letter improvement vs. 5 letters for those with <20/40 BCVA and 1 letter in those with ≥20/40. Through 12 months, the most common ocular serious adverse events were inflammation (2.9 to 5.8 percent), cataract (3.8 percent) and medication residue (transient drug depot in the visual axis; 2.3 percent).

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By Gregory Stein, MD, and Philip J. Rosenfeld, MD, PhD

Next-Generation Therapies For Wet AMD: Upgrade 2.0

Making the case for combination therapies.

Over the past 11 years, we've enjoyed phenomenal success in the treatment of exudative eye diseases, particularly neovascular (wet) age-related macular degeneration, compared with the time before anti-vascular endothelial growth factor (anti-VEGF) therapy.

Anti-VEGF therapy has been one of the most significant breakthroughs in modern medicine, allowing patients the opportunity to improve their vision and stave off blindness over the short term and slow down vision loss over the long term.

But now, patients aren't satisfied with these short-term gains, and we shouldn't be either. Not only does anti-VEGF treatment require frequent office visits with injections, but the long-term data show a relentless loss of vision that is unacceptable to our patients who are living healthier, longer lives.[1]

The two major upgrades being investigated with anti-VEGF therapy include drugs that provide predictable, sustained improvement in visual acuity and treatments that result in fewer clinic visits and injections. To address these unmet needs, the next generation of therapies in clinical trials are exploring agents and combinations that should result in better visual acuity and require fewer injections (*Table, page 14*).

VEGF Is Not Alone

In addition to VEGF, a number of angiogenic growth factors contribute to the molecular milieu that promotes neovascularization.[2] The VEGF family has long been considered one of the main culprits in the formation of neovascularization. The VEGF family consists of VEGF-A, B, C, D and placental growth factor (PIGF), all of which are proteins that interact mainly through VEGFR-2 tyrosine kinase.

VEGFR-2 expression on endothelial cells increases during angiogenesis.[3] This has served as the basis for our current therapies, including bevacizumab and ranibizumab (Avastin and Lucentis, Genentech) which target VEGF-A, and aflibercept (Eylea, Regeneron), which targets VEGF-A and B and PIGF.

Quotable

Patients aren't satisfied with these short-term gains, and we shouldn't be either.

Many other molecular components are critical for neovascularization. For example, platelet derived growth factor (PDGF) is involved in a wide range of biological processes, including angiogenesis, and may likely contribute to neovascularization in wet AMD.[4,5]

The PDGF family consists of PDGF-AA, BB, CC and DD. PDGF interacts with PDGFR-α and PDGFR-β tyrosine kinases, which are found in mesenchymal cells. In particular, PDGFR-β is expressed in vascular smooth muscle cells and pericytes.[6]

Targeting PDGF

Pegpleranib (Fovista, Ophthotech) is an aptamer that binds to PDGF-BB and prevents PDGF from binding to its receptor, PDGFR-β, on pericytes, causing pericytes to be stripped from newly formed abnormal blood vessels.[7]

Pegpleranib has been used in combination with ranibizumab in a Phase I clinical trial, and shown to be safe. The impression from this Phase I trial was that combination therapy resulted in greater regression of the classic component of choroidal neovascularization than the occult component.[8]

Based on these observations, a larger Phase II trial investigated monthly pegpleranib and ranibizumab in combination compared with ranibizumab alone for classic-containing neovascular lesions.

After six months, the combination arms had better visual acuity outcomes compared with ranibizumab. This Phase II study set the stage for the on-going Phase III trials to compare the combination of pegpleranib with ranibizumab, bevacizumab or aflibercept, depending on the study, with the anti-VEGF drug alone.

Topline results from these Phase

TABLE Combination Therapies for Wet AMD in Active Clinical Trials

Compound	Mechanism	Phase	Delivery	Sponsor	Trial Number
E10030 (Fovista/ Pegpleranib)	Aptamer that binds to PDGF-BB	III	Intravitreal	Ophthotec Corporation	NCT01944839 NCT01940900 NCT01940887
OHR-102 (Squalamine)	Small molecule that binds to intracellular calmodulin, inhibiting VEGF, PDGF and bFGF	III	Topical	Ohr Pharmaceutical Inc.	NCT02511613
X-82	Small molecule dual inhibitor of VEGFR and PDGFR	II	Oral	Tyrogenex	NCT01674569
DE-120	Small molecule dual inhibitor of VEGFR and PDGFR	II	Intravitreal	Santen	NCT02401945
REGN910-3 (Nesvacumab)	Monoclonal antibody against ANG2, co-formulated with aflibercept	II	Intravitreal	Regeneron/ Bayer	NCT02713204
REGN2176-3 (Rinucumab)	Monoclonal antibody against PDGFR-β, co-formulated with aflibercept	II	Intravitreal	Regeneron/ Bayer	NCT02418754
RG7716	Bispecific antibody that binds to VEGF-A and ANG2	II	Intravitreal	Hoffman-La Roche	NCT02484690
hI-con1	Factor VII-IgGFc chimeric protein that binds to TF	II	Intravitreal	Iconic Therpaeutics Inc.	NCT02358889
OPT-302	Fusion protein that binds VEGF-C & VEGF-D	I/IIA	Intravitreal	Ophthea	NCT02543229
PAN-90806	Small molecule VEGFR antagonist	I	Topical	PanOptica Inc.	NCT02022540

KEY: PDGF = Platelet-derived growth factor; VEGF = Vascular endothelial growth factor; bFGF = basic fibroblast growth factor, ANG = Angiopoietin, TF = Tissue factor
Table does not include combination therapies that include steroids or radiation.

III studies should be known in the fourth quarter this year. Pegpleranib may be one of the first anti-PDGF agents and a component of the first combination therapy approved.

Rinucumab (Regeneron) is a monoclonal antibody intended to bind to the PDGF-β receptor, preventing the action of PDGF.[9] This drug is in a Phase II study and is being used in combination with aflibercept in a co-formulated single injection.

X-82 (Tyrogenex) is a small-molecule dual inhibitor of VEGF and the PDGF receptor tyrosine kinases.[10] X-82 is in a Phase II study as a once-daily oral formulation in combination with bevacizumab, ranibizumab or aflibercept.

DE-120 (Santen Pharmaceutical) is also a small molecule that inhibits both VEGF and PDGF receptor tyrosine kinases.[11] A Phase IIA study is investigating it as intravitreal monotherapy as well in combination with aflibercept.

The ANG Pathway

Angiopoietin (ANG) is involved in another prominent pathway leading to angiogenesis and has been implicated in the pathogenesis of wet AMD. Angiopoietins are protein ligands that control angiogenesis and vascular stability by interacting with

Tie1 and Tie2, which are receptor tyrosine kinases that are found on endothelial cells.[12,13]

Nesvacumab (Regeneron) is a monoclonal antibody directed against ANG 2 and prevents its interaction with Tie2.[14] It is currently in a Phase II study and is being used in combination with aflibercept in a co-formulated single injection.

RG7716 (Hoffmann-La Roche) is a bispecific antibody that binds both VEGF A and ANG 2.[15] It is in a Phase II study and is being used in combination with ranibizumab.

Target: Tissue Factor

Tissue factor (TF) is another target for wet AMD therapy. TF is well known as a surface receptor for coagulation factor VII, which initiates the extrinsic coagulation pathway.[16] TF has been shown to be upregulated in wet AMD[17] and cancer, and is believed to also promote angiogenesis.[18] Hl-con1 (Iconic Pharmaceuticals) is a factor VII-IgG chimeric protein that binds to TF with the factor VII component, while the IgG component triggers an immunological cascade that destroys the neovascular lesion.[19] It is currently in a Phase II study where it is being used as a monotherapy or in combination with ranibizumab.

Other anti-VEGF medications are in clinical trials and being used in combination with current intravitreal medications. Opt-302 (Opthea) is a fusion protein that binds VEGF-C and VEGF-D, blocking their interaction with VEGFR-2 and VEGFR-3.[20] This strategy is combined with current medications that primarily target VEGF-A. This drug is in a Phase I/IIA study and is being used as both monotherapy and in combination with ranibizumab.

Two topical therapies are currently in clinical trials. Squalamine (Ohr Pharmaceutical) is a medication that targets intracellular calmodulin to inhibit the downstream effects of VEGF, PDGF and basic fibroblast growth factor (bFGF).[21] A topical formulation of this drug is in a Phase III study and is being administered in combination with ranibizumab.

A topical anti-VEGF medication known as PAN-90806 (PanOptica) is being used in combination with intravitreal ranibizumab and is in a Phase I study.[22]

The Future: Anti-VEGF-Plus

For years to come, intravitreal injections with our current anti-VEGF medications will remain the cornerstone of our treatment strategy. However, combination therapies to reduce the injection frequency and improve visual acuity outcomes show great promise to shake up our current treatment paradigm.

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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. Stein is a post-doctoral fellow in medical retina at Bascom Palmer.

Managing High-Risk Asymptomatic RRD

Navigating a management dilemma in this young surgeon who had LASIK.

By Grace C. Shih MD, Jeffrey J. Tan, MD

A 34-year-old female surgeon presented to the University of Southern California Roski Eye Institute for routine yearly follow-up. Her ocular history included 6 D of myopia treated with bilateral LASIK four years prior.

During screening for LASIK, an operculated retinal hole OS in the superotemporal periphery was incidentally discovered. The hole was immediately treated with barrier laser retinopexy. Several months later, she underwent uneventful LASIK surgery and was advised to have yearly dilated retinal exams. She also received education about the warning signs for retinal detachment. At this time, she denied any vision changes, scotomata, flashes, floaters, visual field defects or any other ocular symptoms.

Examination

Uncorrected visual acuity was 20/20 in both eyes, with intraocular pressures of 10 mmHg bilaterally. No afferent pupillary defect was present. Confrontational visual fields were full in both eyes. Slit lamp examination showed well-healed LASIK flaps in both eyes, and was otherwise unremarkable.

Dilated fundus examination was unremarkable in the right eye and significant for a superotemporal mid-peripheral operculated retinal hole in the left surrounded by a ring of pigmented scars, with shallow subretinal fluid (SRF) extending beyond the laser scars to the edge of the macula.

Diagnosis, Workup, Treatment

Given her exam findings, we informed the patient of her diagnosis of superior macula-sparing rhegmatogenous retinal detachment (RRD) OS. Upon further detailed questioning, we confirmed that she was entirely asymptomatic. We discussed various treatment options with her, including further barrier laser, pneumatic retinopexy with either cryotherapy or laser, primary scleral buckle, vitrectomy or close observation.

Ultimately, the patient was offered immediate supplemental laser retinopexy, with the hopes that laser uptake in the area of shallow SRF would result in an adherent chorioretinal scar. During the procedure, there was some uptake at the temporal margin of the SRF; however, uptake was poor in the area of SRF most threatening to the macula (*Figure 1*). We asked the patient to limit her activity and follow up in one week, sooner in case of any suspicious symptoms.

At one-week follow-up, she was still asymptomatic, and the SRF was roughly stable. Some of the fresh laser marks superotemporally were beginning to show pigmentation, but there was still significant SRF threatening the macula.

The risks, benefits, and alternatives to various treatment strategies were again discussed with the patient. We also asked her to seek a second opinion with another respected retina expert, which she did. Given her young age, occupation requiring stereopsis, phakic status, history of refractive surgery and vitreomacular adhesion as seen on optical coherence tomography (*Figure 2*), we offered her primary scleral buckle.

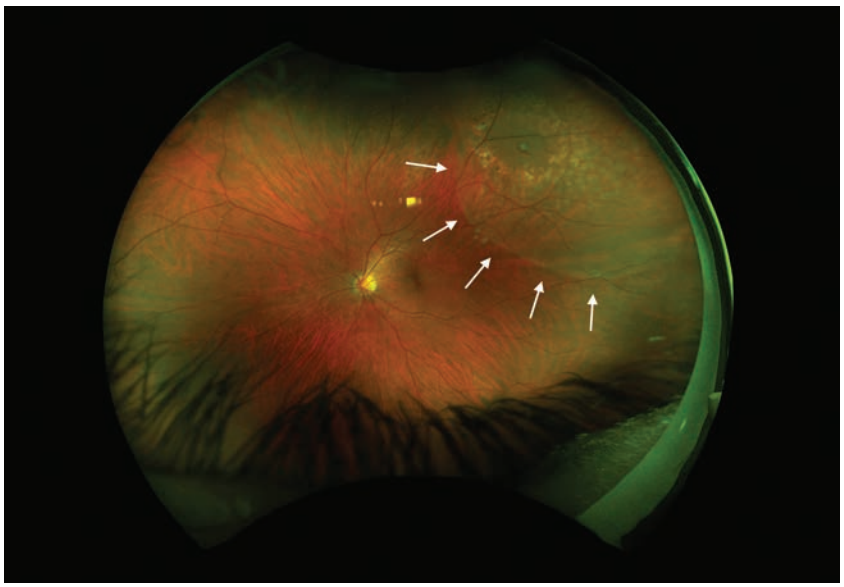

Figure 1. Widefield fundus photography of the left eye shows a superotemporal operculated retinal hole surrounded by prior laser retinopexy scars, with a shallow cuff of subretinal fluid (arrows) extending beyond the laser scars.

Some advantages of this approach for this patient included maintenance of good visual acuity postoperatively, avoidance of the need for postoperative positioning and decreased risk of cataract progression.

During surgery, we identified and marked the retinal break, applied cryotherapy and placed a 240 encircling band with a 276 segmental tire to ensure support of the break, which was relatively posterior in location, approximately 7-8 mm behind the rectus muscle insertions. Given that the SRF was quite shallow, we did not undertake external drainage.

On postoperative day one, the retinal break was well supported and fresh cryotherapy marks could be seen surrounding it. Shallow SRF remained (*Figure 3A, page 18*). At postoperative month two, the SRF had entirely resolved, and the cryotherapy scars had matured to become pigmented (*Figure 3B*). At this visit, the patient achieved 20/20 visual acuity with a -2.25 D spherical refraction. The patient's refractive outcome left her with functional monovision, and she was able to adapt well to a contact lens OS.

Discussion

In the management of a retinal detachment, various options are at the physician's disposal. However, the treatment of asymptomatic macula-sparing rhegmatogenous detachments remains highly controversial. Ranging from intraocular surgery to observation, decisions are often made on a case-by-case basis, as no single treatment has been unequivocally demonstrated to be superior to the others. Here we review the five primary options.

Observation. Advocates of observation propose that the risks of therapy may outweigh the presumable benefit of preventing future symptomatic problems. Among other reasons, proponents note that possible consequences of retinal detachment surgery include cataract formation, glaucoma, bleeding, infection, choroidal effusion, cystoid macular edema, macular pucker, diplopia, refractive shift and proliferative vitreoretinopathy.[1]

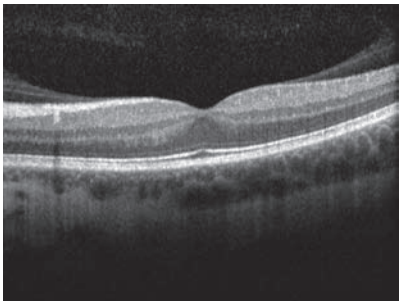

Figure 2. Optical coherence tomography of the left eye showed vitreomacular adhesion.

In a single-observer, prospective observational case series of 18 eyes, Steven Cohen, MD, found that the natural history of asymptomatic retinal detachments over an average of 46 months of follow-up was to remain asymptomatic and stable for four years, with only one incidence of slight progression that subsequently stabilized.[2] He thus concluded that asymptomatic, clinically diagnosed rhegmatogenous retinal detachments can be safely observed on the order of years.

Similarly, Norman Byer, MD, reported two cases of subclinical retinal detachments spontaneously regressing and resolving, with no recurrence in 12-14 years.[3] His prospective, natural history cohort study of 19 eyes with asymptomatic retinal breaks likewise found a less than 1 percent per year incidence of progression to clinical retinal detachment.[4] A study of 31 eyes with asymptomatic retinal detachments only found two eyes that progressed into symptomatic detachments at two and three years following initial detection,[5] and the authors similarly concluded that observation and patient education were reasonable management strategies for this group of patients.

In contrast, Matthew Davis, MD, who defined subclinical retinal detachments as flat detachments extending more than 1 disc diameter from a retinal break, but no more than 2 DD posterior to the equator, has supported the argument for prophylactic intervention. In his analysis of 20 eyes with asymptomatic subclinical detachments followed for six months or more, six of the eyes progressed to clinical retinal detachment.[6,7] Similarly, W.H. Jarrett, MD, found progression of retinal detachments in seven of 15 eyes with asymptomatic macula-on retinal detachments during follow-up of up to 10 months.[8]

Laser retinopexy. In a study of asymptomatic macula-sparing retinal detachments, demarcation laser photocoagulation of shallow RRD without associated proliferative vitreoretinopathy (PVR) was found to be a reasonable alternative to surgical repair, even in eyes with well-established risk factors for progression, including horseshoe tears, vitreous hemorrhage or RRD in the fellow eye.[9] As an in-office procedure without the risks of intraocular surgery, demarcation laser photocoagulation is often employed as a primary treatment of asymptomatic retinal detachments.

However, patients must be warned of the potential need for further intervention if the laser barricade is insufficient for blockage of subreti-

nal fluid progression, especially since it takes up to two weeks for the chorioretinal adhesions to fully form.

Laser has theoretical advantages over cryotherapy by inducing less inflammation, discomfort and retinal pigment epithelium dispersion, thereby decreasing risk for epiretinal membrane and PVR formation. Our patient initially underwent laser, but we ultimately felt it was insufficient to reduce the risk of progression.

Pneumatic retinopexy. As a non-incisional treatment option for retinal detachment repair, pneumatic retinopexy was initially advocated for breaks located within 1 o'clock position from the superior two-thirds of the retina.

Additionally, phakic patients were found to have better outcomes with pneumatic retinopexy.[10] Since then, the indications for pneumatic retinopexy have grown to include multiple breaks in multiple quadrants.[6,11] This procedure is minimally invasive, may be conducted in the office setting, has reduced recovery time and has excellent postoperative visual acuity results.[12]

However, several studies have demonstrated a statistically lower rate of reattachment with pneumatic retinopexy in comparison to primary scleral buckling.[10,13] Additionally, failures after pneumatic retinopexy feature the more prominent risk of PVR that can be visually devastating.[14] Younger patients may have a higher risk of PVR formation.[15]

Patient selection is imperative to the success of the procedure, with ocular, physical and social considerations arguably playing a larger role in the decision-making process than in other procedures. The surgeon must choose whether to employ pregas injection cryotherapy or post-gas injection laser as a method of retinopexy, further complicating decision-making.

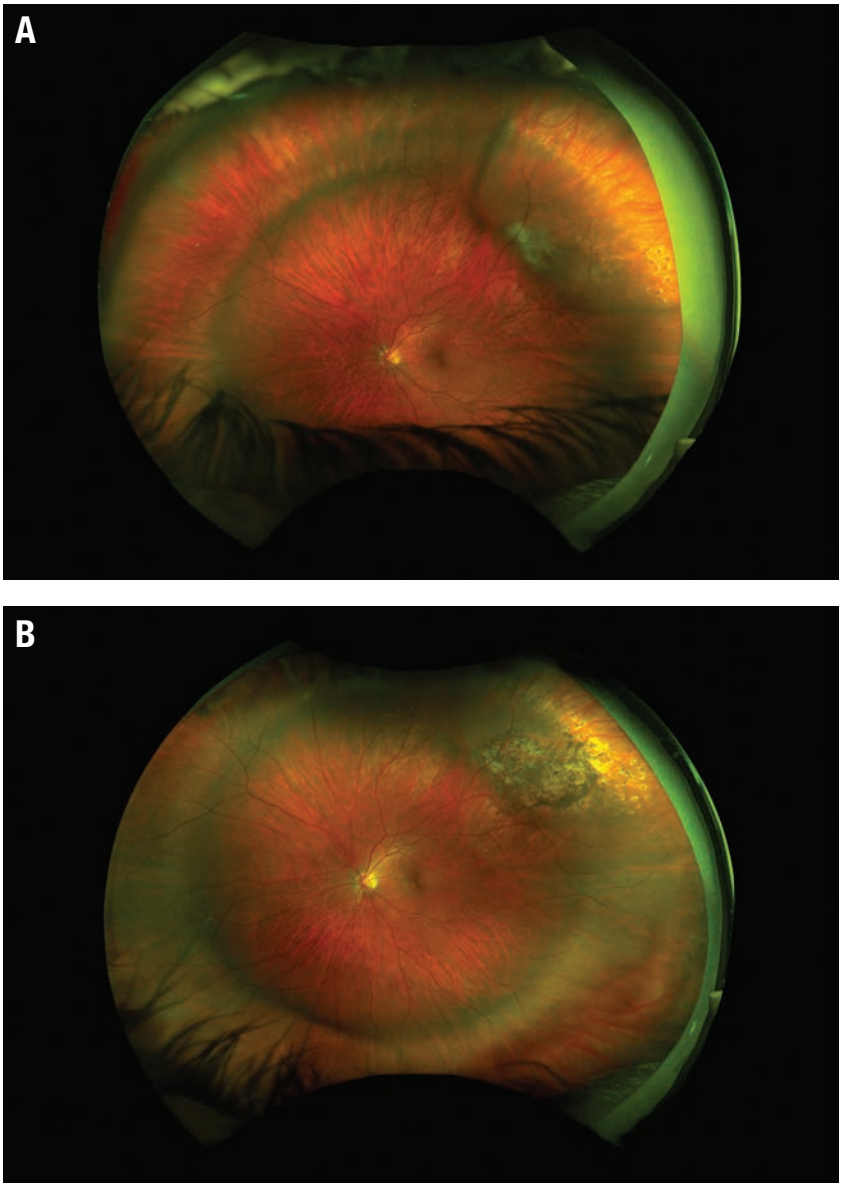

Figure 3. Widefield fundus photography of the left eye (A) first day postoperatively shows shallow subretinal fluid (SRF), scleral buckle indentation and fresh cryotherapy marks. At two months postoperatively (B), fundus photography shows resolution of SRF and pigmented cryo scars.

Scleral buckle. Scleral buckling (SB) has long been considered the gold standard for uncomplicated RRD repair, with longstanding stability of up to 95 percent reattachment at 20 years.[16] Benefits of primary SB include long-term support of the vitreous base and less risk of endophthalmitis, cataract progres-

sion and other complications of intraocular surgery. Additionally, many SB cases do not require tamponade agents, thus avoiding the need for postoperative positioning and travel restrictions.

However, identification of all retinal breaks and adequate visualization is crucial for surgical success, and a combination of explants, chorioretinal adhesion techniques and drainage of sub-retinal fluid must be employed tactically.

Moreover, induced myopia is inevitable with an encircling band, with various studies citing average spherical equivalent changes of -1 D to -2.75 D.[17,18] In our patient's case, SB enabled faster visual and activity recovery while maintaining good long-term visual outcome.

The most commonly reported causes of primary SB failure include PVR and choroidal detachments, although the Pseudophakic and Aphakic Retinal Detachment Study Group demonstrated a similar frequency of choroidal detachments after SB and PPV.[19]

In a retrospective review of 28 eyes with asymptomatic clinical retinal detachments that underwent scleral buckling, all patients had excellent anatomic and visual results.[20] However, this study lacked a control group for comparison.

Pars plana vitrectomy. With a 71 to 92 percent primary success rate, and a 92 to 95 percent final success rate, PPV is an excellent treatment option for RRDs.[21,22] With good visualization of all tears and breaks, as well as the removal of opacities and vitreous traction, this procedure allows for excellent anatomic success in complicated detachments.[12]

However, in young patients like ours without a pre-existing PVD, PPV is often more challenging. Risks of this intraocular surgery include iatrogenic retinal breaks, PVR, lens trauma and cataract progression,[17,23] as well as prolonged postoperative positioning requirements. One might argue that these factors may make vitrectomy the suboptimal choice in an otherwise asymptomatic young patient.

The Decision for Our Patient

Ultimately, the specific clinical situation at hand dictates the management of asymptomatic retinal detachments. This can only be informed from a thorough discussion of risks, benefits and expectations for each possible strategy with affected patients.

The decision to treat our patient was prompted by the high-risk location of her detachment superotemporal to the fovea and her need for stereopsis to continue practicing as a surgeon. The decision for scleral buckle was based upon the patient's young age, phakic status and need for rapid visual rehabilitation. As in this case, the decision-making process must involve a multifaceted approach and employ the art, as well as the science, of medicine. RS

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By Paul Hahn, MD, PhD »

A Novel Approach for Surgical PVD

This hydrodissection approach avoids risks of iatrogenic retinal tears and optic nerve traction. ***With Vincent Y. Ho, MD, and Gaurav K. Shah, MD***

I thought we all did it the same way. Surgical posterior vitreous detachment (PVD) induction involved high vacuum at the edge of the optic nerve followed by slow elevation to induce centripetal separation, right? At the recent Ocular Imaging Conference WAVE 2016 meeting in Vail, Colo., it was proposed that this approach may induce excessive traction at the retina and even the optic nerve, and I learned an alternative, potentially safer approach to surgical PVD.

In this pearl, Vincent Y. Ho, MD, and Gaurav K. Shah, MD, present "hydrodissection PVD," their preferred method of surgical induction that they propose minimizes traction at the optic nerve and retina and reduces the risk of iatrogenic retinal tears.

Step by Step

First, apply kenalog to highlight the vitreous, then hold the vitrector near a temporal vascular arcade port-down (facing the retina) with maximum aspiration (no cutting) to engage a portion of the posterior hyaloid. Maintain maximum aspiration until a space appears between the posterior hyaloid and retina.

The next step is to initiate cutting along with maximum aspiration. Use the vitrector with the port still facing downward to create a 360-degree circumferential hyaloidectomy at the level of the midperiphery. In doing so, the vitreous flows anteriorly into the vitrector port while the infusion fluid is forced posteriorly, resulting in hydrodissection of the remaining posterior hyaloid off the retinal surface and out to the vitreous base insertion.

Typically, the last hyaloid remnant is attached to the nerve, and you can remove it by slowly approaching the posterior pole with the vitrector. Once the posterior vitreous detachment is complete, turn the port to face the vitreous base for peripheral shaving if indicated.

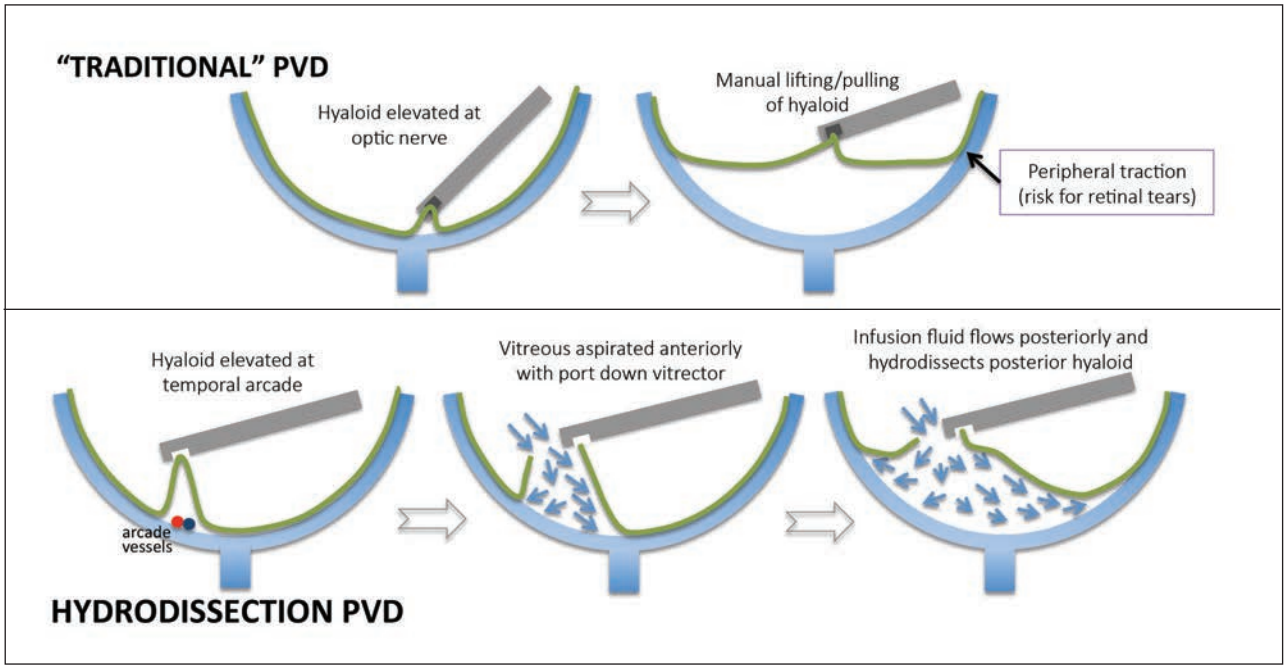
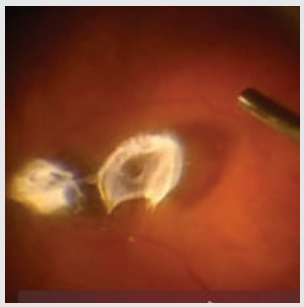


Figure. Traditional posterior vitreous detachment (top) involves manual elevation of the posterior hyaloid from the optic nerve to the periphery, which can lead to peripheral retinal traction and tears. Hydrodissection PVD begins with aspirating a portion of the posterior hyaloid over a temporal vascular arcade with the port down. Once space is created, vitrectomy is performed 360 degrees circumferentially in the mid-peripheral vitreous with the port down and full vacuum. As vitreous aspirates anteriorly, infusion fluid flows posteriorly, gently hydrodissecting the hyaloid off the retina to the vitreous base.

Reduction of Risks

Because this approach uses primarily hydrodissection to separate the hyaloid, as opposed to direct traction with the traditional method, Drs. Ho and Shah believe it reduces the risk of iatrogenic retinal tears and optic nerve traction. They use an EVA by DORC (Exeter, N.H.) vitrectomy platform with 92 percent biased-open duty cycle and augmented infusion that create robust and dynamic flow that they feel is critical to the success of this maneuver. This technique works best in vacuum mode (rise time up to 300 milliseconds, maximum vacuum of 680 mmHg), and can successfully be completed with 20-, 23-, 25- and 27-gauge surgery.



Watch the Video

Watch as Vincent Ho, MD, and Gaurav Shah, MD, describe a novel approach to potentially safer posterior vitreous detachment induction using hydrodissection. Available at: http://bit.ly/2aWlzk7

PVD induction is routine, but can be associated with retinal breaks that we generally accept as unavoidable. This pearl demonstrates the use of advancing technology and improved fluidics to develop a potentially safer approach compared to the conventional maneuver. Maintaining multiple approaches is important for successful completion of even "routine" surgical maneuvers. For patients at high risk for iatrogenic tears during PVD induction, hydrodissection PVD may be worth a try.

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Focus on Imaging

WILL OCT ANGIOGRAPHY REPLACE FA?

A close look at how this emerging imaging modality compares with the gold standard.

By Talisa E. de Carlo, MD, and Caroline R. Baumal, MD

Optical coherence tomography angiography (OCTA) is a novel technique for non-invasive, non-dye-based imaging of retinal and choroidal circulation.[1,2] The en-face OCT angiogram images are depth-resolved and can be segmented to image flow in the superficial, intermediate and deep retinal capillary plexuses, the outer retina (which normally has no flow) and the choriocapillaris.

Multiple spectral-domain and prototype swept-source-based OCTA devices are available. They vary somewhat in hardware and software components. The OptoVue AngioVue (Fremont, Calif.) and the Zeiss Angioplex (Carl Zeiss Meditec, Dublin, Calif.) are Food and Drug Administration-approved for OCTA.

The common principle OCTA uses to acquire the image is motion contrast detection. The device notes differences between multiple, rapidly repeated OCT B-scans at each individual cross-section of the retina and assumes them to be due to erythrocyte movement within blood vessels. These "decorrelation signals" create a vascular map called an OCT angiogram (*Figure 1*).[1] The OCT angiogram and OCT B-scans are then co-registered for simultaneous visualization of both structural and vascular information.

Are Devices Upgradeable?

A common question retina specialists ask is whether their current OCT systems can be upgraded to perform OCTA. That depends on the system itself and its age. The most likely answer is no. The typical OCT device requires more than just a software update with the decorrelation algorithm in order to do OCTA.

Most notably, OCTA requires much higher scanning speeds because of the need for multiple consecutive OCT B-scans. Conventional scanning speeds of 26,000 to 40,000 A-scans per second would result in a trade-off between decreased resolution/quality, decreased field of view and increased acquisition time. For that reason, scanning speeds at least twice as fast (upwards of 70,000 A-scans/second) are desirable for OCTA so that at least two repeated B-scans can be obtained at each cross-section without changing resolution, field of view or acquisition time. Furthermore, even faster imaging speeds allow for more than two repeated B-scans per cross-section, which can improve the signal-to-noise ratio.

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DISCLOSURES: The authors' work has been supported in part by an unrestricted grant from the Massachusetts Lions Club. Neither Dr. de Carlo nor Dr. Baumal have any relevant disclosures.

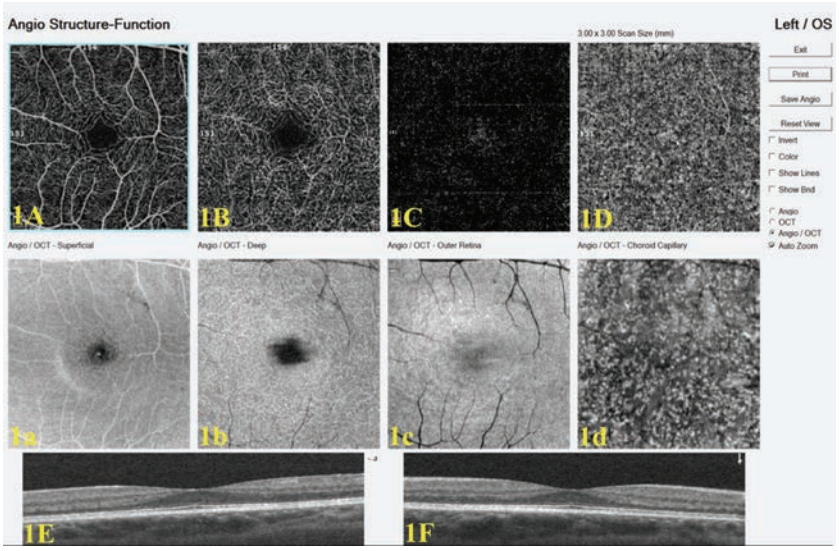

Figure 1. Overview printout, OptoVue Avanti of a normal left eye showing the optical coherence tomography angiography segmentation (A-D), en-face OCT segmentations (a-d), and two corresponding OCT B-scans (E-F) that each OCTA scan set creates. OCTA and en-face OCT images are automatically segmented to show the superficial retinal capillary plexus (A, a), deep retinal capillary plexus (B, b), outer retina (C, c) and choriocapillaris (D, d). Note the homogeneity of each plexus, the lack of blood flow in the outer retina and the small round foveal avascular zone.

OCT angiogram resolution depends on how many A-scans comprise a specific field of view, as the device automatically interpolates information between any two points. The fewer the A-scans in a set area, the more interpolation needed in the spaces between the A-scans and, therefore, the more likely the scan will miss subtle changes. As OCTA is based on motion detection, the acquisition time is limited by how long the patient can keep his or her eye open without blinking.

The machine cannot detect movement when the patient closes the eye, so the OCT angiogram will be marked with a black horizontal or vertical line (complete "absence" of flow).[1] Thus, the slower scanning speeds of conventional OCT devices would either result in greatly reduced resolution, a field of view so small that it would be clinically useless, and/or OCT angiograms with black lines across them.

Static OCTA vs. Dynamic FA

Many differences exist between how fluorescein angiography (FA) and OCTA devices obtain images and the type of information they provide (*Table, page 25*). FA has long been the gold standard for posterior segment vascular imaging. It requires intravenous dye administration and produces a two-dimensional image showing details primarily comprised of the superficial retinal capillary plexus. However, FA imaging of the radial peripapillary network, deep retinal capillary plexus and choroidal vasculature is poor.[3] FA image interpretation is based on dynamic properties of dye leakage, staining and blockage.[1]

With ultra-widefield FA, the imaging field can encompass the entire macular region or extend beyond the equator. The FA technique can be limited by its more expensive technical requirements, time constraints, invasive nature and risk of allergic reaction to the fluorescein dye, ranging from nausea to, rarely, death from anaphylactic shock.

In contrast, OCTA is non-invasive and provides static volumetric angiographic information depicting a snapshot in time of blood flow. OCTA provides highly detailed images of flow in the superficial retinal capillary plexus in addition to the intermediate and deep retinal capillary plexuses, the radial peripapillary network and choriocapillaris. The corresponding OCT B-scans are co-registered with the OCT angiograms, revealing the structural anatomy and corresponding flow respectively.

The OCTA field of view is more limited than FA; the most common utilized OCTA scanning size is 3 by 3 mm, which researchers estimate is at least as detailed, or more so, than

Take-Home Point

Retina specialists primarily use fluorescein angiography to image the retinal vasculature and choroidal neovascularization, and indocyanine green angiography to image choroidal disorders. Optical coherence tomography angiography has emerged as an imaging modality that produces segmented images of both the retinal and choroidal vascular flow, to be viewed in tandem with the corresponding structural OCT B-scans from the same region. Thus, OCTA distinguishes itself with its ability to simultaneously evaluate diseases affecting flow in both the retina and choroid. This non-invasive and fast en-face blood flow imaging modality can obtain high-resolution volumetric data, which increases its potential future utility compared with the more invasive two-dimensional dye-based counterparts. With OCTA, there is certainly much more to come on the horizon.

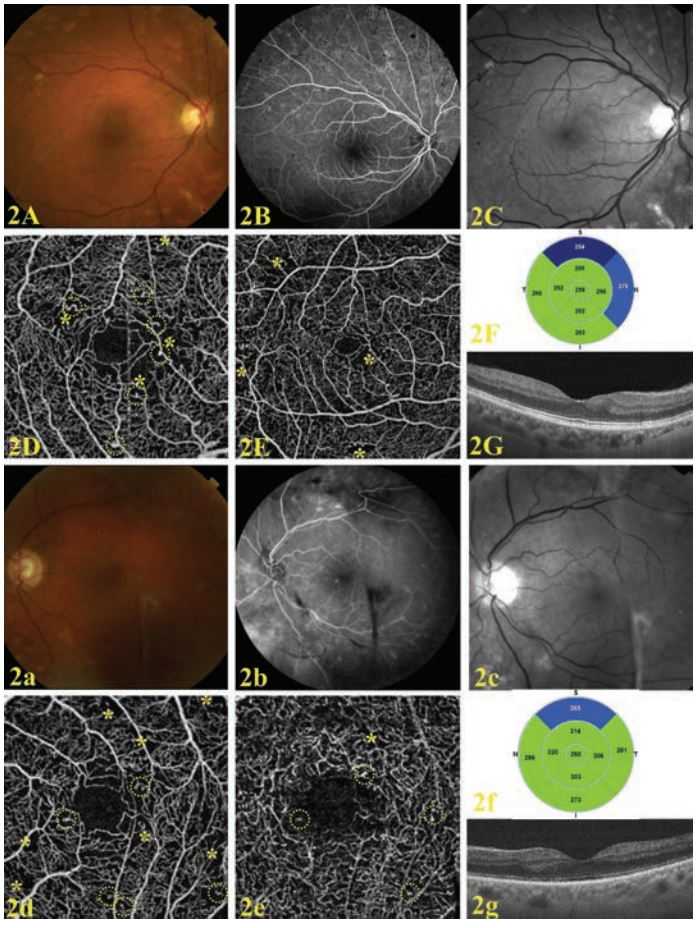

Figure 2. Right eye (A-G) and left eye (a-g) in proliferative diabetic retinopathy. Color photograph (A), intermediate-phase fluorescein angiography (FA; B), and red-free imaging (C) show panretinal photocoagulation in the mid-periphery, macular dot hemorrhages, microaneurysms, preretinal neovascularization and a cotton wool spot superotemporally. Macular 3-by-3-mm (D) and 6-by-6-mm (E) optical coherence tomography angiography shows microaneurysms (circled) and an irregular foveal avascular zone (FAZ) with adjacent and more peripheral areas of capillary non-perfusion (asterisks) that are difficult to appreciate with the other imaging modalities. OCT B-scan shows superonasal thinning (F) and disorganization of the retinal layers perifoveally (G). Color photograph (a), intermediate-phase FA (b), and red-free imaging (c) of the left eye show mid-peripheral panretinal photocoagulation scars and media opacity due to old hemorrhage and microaneurysms. Macular 3-by-3-mm OCTA images of the superficial (d) and deep (e) retinal capillary plexuses show microaneurysms (circled) and an irregular FAZ with adjacent and more peripheral areas of capillary non-perfusion (asterisks). OCT B-scans show superior thinning (f) and disorganization of the retinal layers perifoveally (g).

high-resolution FA imaging. Larger scan sizes up to 12 by 12 mm are possible; however, in most current devices the image resolution would subsequently be reduced because it inversely relates to the field of view. Software is being developed to stitch together or montage the detailed 3-by-3-mm OCTA images to increase the field of view without compromising image resolution.[4]

The OCTA image is based on flow detection by assuming that all motion is secondary to red blood cell movement in the vasculature. This makes OCTA images very sensitive to extraneous patient movement, fixation ability and ocular saccades, so each machine requires some motion correction or eye-tracking technology. OCT displays gross eye motion as bright white horizontal or vertical lines across the angiogram.

Motion-correction software automatically compensates for minor eye movements and merges two image sets to theoretically remove these lines. However, in cases with significant movement, the motion-correction software can create other artifacts while correcting for motion, such as vessel doubling, a quilting pattern or loss of detail.

Imaging with OCTA is fast. A typical imaging session on one eye takes about one second to obtain the X-fast scan, and then one second to obtain the Y-fast scan; it takes a total of about one minute to merge these two orthogonal scans and apply motion correction to the final OCTA volume. Therefore, total imaging time from the moment the patient places and adjusts his or her head in the chin rest to the processing and viewing of bilateral image sets takes about five minutes, in stark contrast to the 20 or more minutes for dye-based angiography. However, poor visual acuity and limited fixation in some cases may affect the quality of the image, more so with OCTA than with FA.

OCTA in Macular Telangiectasia

One of the initial disorders for which clinicians used OCTA is macular telangiectasia type 2. OCTA images are more revealing than FA, showing vascular rarefication or dilation, telangiectasia, neovascularization and decreased capillary density more prominently in the deep retinal capillary plexus.[5] Because OCTA is depth-resolved, volume rendering can aid in visualizing the vascular flow three dimensionally, allowing for more dynamic evaluation that retains its sense of depth.

This is the technique that Richard Spaide, MD,

and co-authors used to illustrate that neovascularization in macular telangiectasia type 2 appears to originate from a right-angle vein from the retinal vasculature, causing lateral contraction and diving into the subretinal space.[6] This demonstrates the increased potential utility of OCTA in this disorder, as FA mainly images the superficial retinal capillary plexus and thus cannot evaluate the deep retinal capillary plexus in such detail.

Fluorescein Angiography vs. OCT Angiography

Fluorescein Angiography	Optical Coherence Tomography Angiography
Widefield capabilities	Field of view limited to 12 by 12 mm
Invasive	Non-invasive
Dye-based	No dye used
Lower resolution	Higher resolution
Less affected by motion	More affected by motion
Two-dimensional; segmentation not possible	Three-dimensional; segmentation possible
Images superficial retina	Images superficial, deep and outer retina, and choroid
Dynamic blood flow information	Static blood flow information
5-30 minutes of imaging time	< 5 minutes of imaging time

Uses in Diabetic Retinopathy

Diabetic retinopathy has been well described with OCTA. Compared with FA, OCTA provides greater detail of most microvascular abnormalities, such as an enlarged irregular foveal avascular zone (FAZ), capillary non-perfusion and intraretinal microvascular abnormalities (*Figure 2*).[7] OCTA shows that the FAZ and perifoveal intercapillary areas are enlarged with each advancing stage of retinopathy. One exception is that microaneurysms may be more readily visualized with FA due to the contrast of pooled and/or slowly leaking fluorescein dye on an otherwise dark background with minimal microvascular detail.[8]

In contrast, the greater detail of the surrounding microvasculature that OCTA obtains makes these subtle aneurysmal dilations more difficult to distinguish from surrounding vessels. Furthermore, microaneurysms may not be patent or absent, or the flow of red blood cells may be too slow to detect with OCTA.[1] Microaneurysms noted on FA correspond to capillary loops as well as focal vascular dilations on OCTA, and their exact intraretinal location can be determined with OCTA segmentation.

OCTA can readily image preretinal neovascularization in proliferative DR by evaluating en-face images segmented superficially at the vitreoretinal interface (*Figure 3*). Manual adjustment of the automated segmentation lines can accomplish this. Interpretation of DME requires differentiation of intraretinal cystic spaces from capillary non-perfusion. Both of these entities appear as dark areas on OCTA; however, intraretinal cystic areas have rounded edges and are completely black, while capillary non-perfusion appears less dark with sharp irregular edges that follow the retinal vessel borders.

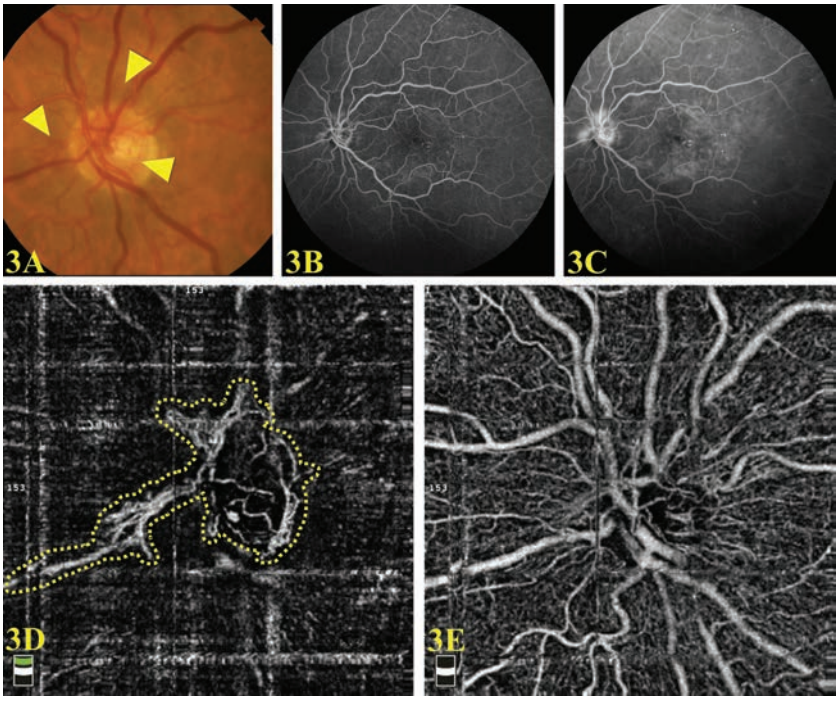

Figure 3. Left eye with proliferative diabetic retinopathy and neovascularization of the disc (NVD) seen as fine abnormal vessels on color photograph (A; arrowheads) and dye leakage between intermediate (B) and late (C) phase of fluorescein angiography. On optical coherence tomography angiography, NVD appears as a flow signal above the internal limiting membrane (D, circled) and above the optic disc (E).

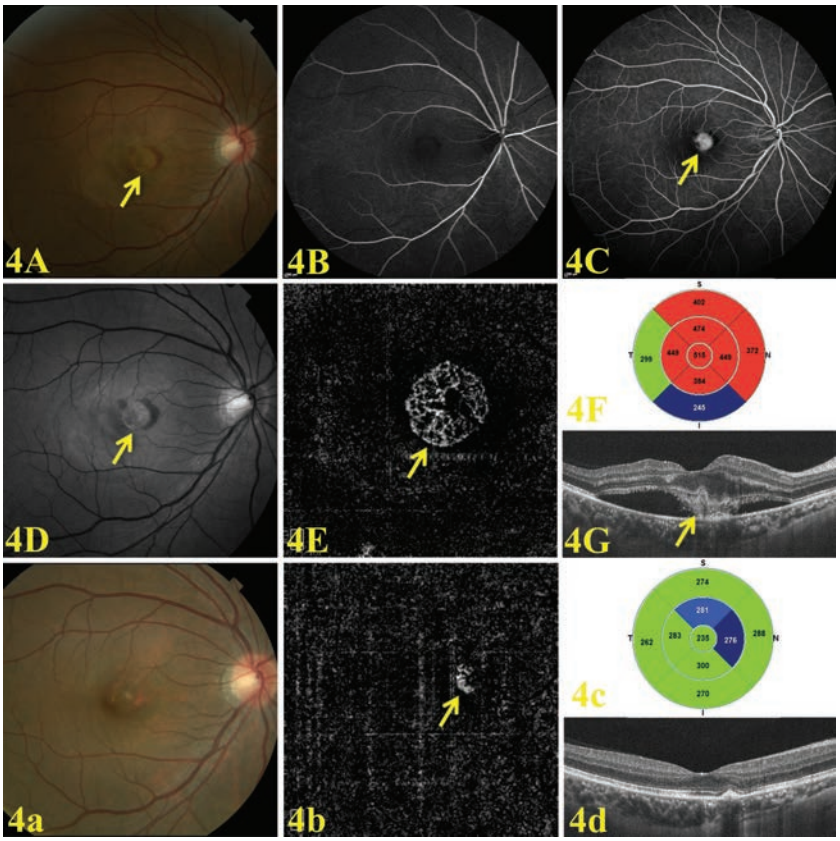

Figure 4. Right eye with choroidal neovascularization (CNV) pre- (A-G) and post- (a-d) intravitreal anti-VEGF injection. Color photo (4A) and red-free (D) show a foveal lesion (arrow) with adjacent hemorrhage and subretinal fluid. Early (B) and late (C) fluorescein angiography demonstrate leakage (arrow) due to type 2 CNV. Macular 3-by-3-mm optical coherence tomography angiography (E) in the outer retina reveals a delicate lacy well-circumscribed sea-fan-shaped foveal CNV (arrow). OCT B-scan shows retinal thickening (F), hyper-reflective tissue (arrow) above the retinal pigment epithelium, and subretinal fluid (G). After treatment, color photograph (a), macular 3-by-3-mm OCTA (b) and OCT (c, d) show resolution of subretinal fluid and reduction of CNV size.

OCTA of Vascular Occlusion

OCTA can demonstrate the features of both retinal artery and venous occlusion sufficiently to establish the diagnosis. In vascular occlusions, capillary telangiectasias, collateral vessels, microaneurysm, capillary nonperfusion and the borders of ischemic retina are well delineated using OCTA.[9] OCTA is at least as detailed as FA imaging, with a handful of publications reporting that OCTA provides increased retinal detail in vascular occlusion.[9,10]

The different vascular plexuses can be segmented using OCTA for enhanced imaging to determine which plexus is more affected. In retinal artery occlusions, the radial peripapillary network can be visualized as it may be preserved or attenuated in chronic cases.[11] This type of imaging is not possible with OCTA in choroidal neovascularization.

This ability to segment the OCT angiograms makes OCTA particularly useful for assessing choroidal neovascularization (CNV) due to exudative age related macular degeneration and other diseases.

Segmentation of the choriocapillaris and/or outer retina can visualize CNV and feeder vessels with high sensitivity and specificity (*Figure 4*).[12,13] Authors have described a variety of CNV configurations, such as a well-circumscribed dense "sea fan" network or poorly circumscribed "long filamentous" CNV.

Furthermore, OCTA may be able to detect early CNV prior to visualization on FA and/or clinical inactivity after therapy. Unsuspected CNV has even been appreciated in eyes with geographic atrophy from non-exudative AMD, which may provide further understanding of this disease process.[14] Because OCTA is non-invasive, it can be repeated frequently to closely monitor treatment response by changes in subretinal and intraretinal fluid as well as CNV size and morphology.[15,16]

After anti-vascular endothelial growth factor therapy, OCTA shows decreased or absent flow in the peripheral and finer CNV vessels, demonstrating a smaller and less dense vascular net. In contrast, CNV appears as leakage on FA, making exact delineation of the vascular net difficult and preventing precise monitoring of CNV size and density.

In polypoidal choroidal vasculopathy (PCV), CNV can be easily visualized using OCTA; however, OCT angiography may inconsistently image the polyps that indocyanine green angiography (ICGA) visualizes.[17] Utilization of cross-sectional OCTA can demonstrate flow signal focally within polyps, improving their detection.[18] OCTA can also help detect CNV in

eyes with chronic central serous chorioretinopathy (CSCR).[13,19]

Authors have used OCTA to show that irregular fibrovascular retinal pigment epithelial detachment (PED) is a risk factor for type 1 CNV in chronic CSCR, and that CNV may be independent of the presence of intraretinal and subretinal fluid.[19] Detection of type 1 CNV with FA can be difficult because of its subtle late leakage.

While FA is the current gold standard for CNV detection, OCTA has been shown to provide clear visualization of CNV in eyes with equivocal FA findings; thus it is useful to confirm subtle cases.[12] In addition to CNV detection, segmentation of the choriocapillaris layer in eyes with CSCR shows foci of reduced flow on OCTA that in some cases may be adjacent to the location of hot spots on ICGA.[20]

OCTA has been used to detect CNV and monitor treatment response in uveitic diseases, including acute zonal occult outer retinopathy, punctate inner choroidopathy and multifocal choroiditis, even when more traditional imaging modalities such as FA show an inactive PED, scar or equivocal findings.[16,21]

Birdshot Chorioretinopathy And Inherited Disease

Researchers at New England Eye Center used OCTA to describe novel findings in birdshot chorioretinopathy (BCR), including disruption of the choriocapillaris below lesions with larger choroidal vessels bordering these areas of non-flow.[22] Furthermore, retinal thinning, telangiectatic vessels, capillary dilations and loops, and grossly increased intercapillary areas were uniquely imaged with OCTA in birdshot eyes—which had not previously been described using other imaging modalities.[22]

The improved resolution of OCTA compared with FA allows for easier visualization of retinal changes in eyes with BCR that older imaging modalities could not detect. OCTA has characterized a variety of less-common disorders, including Coat's disease (*Figure 5*), inherited retinal degenerations, sickle cell disease and orbital tumors.

In inherited diseases such as retinitis pigmentosa and Stargardt disease that have progressive photoreceptor and RPE loss, OCTA shows overlying retinal thinning and increased intercapillary area, FAZ abnormalities and choriocapillaris loss or decreased perfusion below the absent RPE, similar to that seen in geographic atrophy.[23]

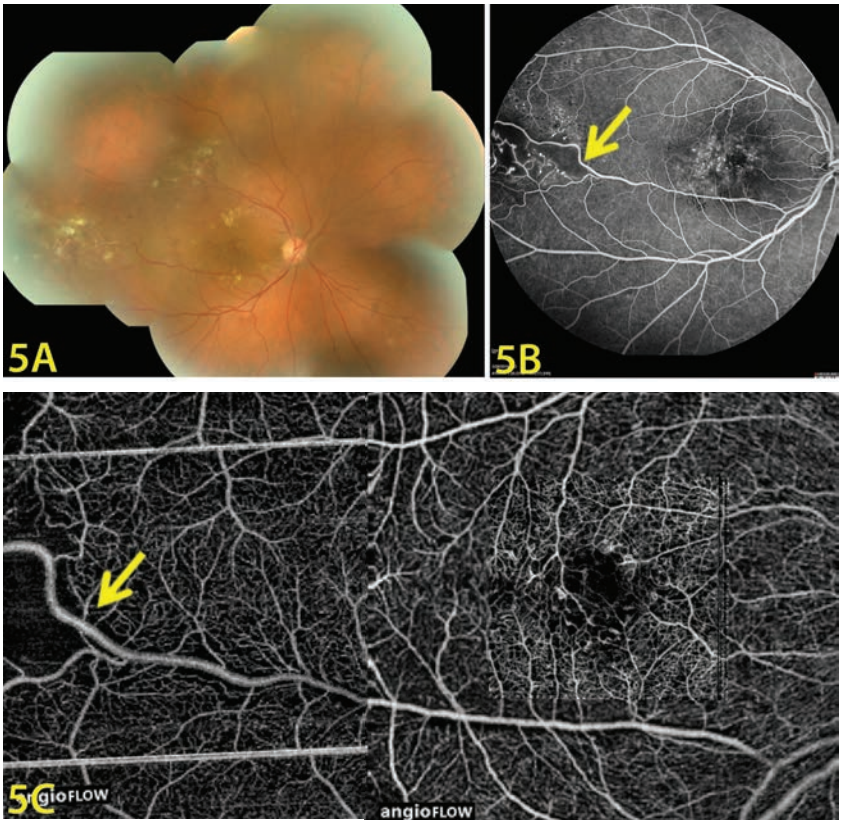

Figure 5. In Coat's disease, color photo of the right eye (A) shows exudation at the arcades and temporally. Fluorescein angiography (B) and a montage of 3-by-3-mm optical coherence tomography angiography images (C) demonstrate microaneurysms in the macula and temporally within and adjacent to an area of capillary non-perfusion.

Actually Doing OCTA

One practical consideration is that the ability to do OCTA imaging on your patients may require the purchase of a new, faster OCT device. Additionally, no modification in billing code for OCTA currently exists beyond that of conventional structural OCT B-scan.

Overall, OCTA has proven to be valuable for diagnosing a variety of retinal disorders and monitoring therapeutic response with findings that may complement or exceed FA imaging in some cases. It is likely that future software and hardware updates will increase the field of view

(Continued on page 37)

Focus on Imaging

TAKING OCT OUT TO THE RETINAL PERIPHERY

How ultra-widefield spectral domain optical coherence tomography gives us a new view of pathology.

By Netan Choudhry, MD, FRCSC, with John Golding

Optical coherence tomography has revolutionized how we interpret macular pathology, but its ability to image pathology of the peripheral retina has been limited. However, using ultra-widefield steering-based spectral-domain OCT, we were able to image 19 different types of features in the peripheral retina, which may give us the potential to follow retinal lesions over time and boost the utility of telemedicine for the management of retinal disease.

OCT traditionally has provided a 30-degree view, staying within the macula. The Diabetic Retinopathy Clinical Research Network identifies widefield OCT as 100 degrees.[1] Our approach with ultra-widefield spectral-domain (UWF SD) OCT has gone out to 200-plus degrees and beyond the level of pars plana.

This imaging has allowed us to see retinal tufts with great detail and traction, the ora serrata pearl and areas of peripheral cystoid degeneration—areas that have not been imaged with SD-OCT in the past.

Here, I share our research team's experience with steering-based, UWF SD-OCT in the clinic, drawing on a study we recently published in *Ophthalmology*[2] and reported at the American Society of Retina Specialists annual meeting.[3] In our study, we imaged 68 eyes and identified 19 different findings in the peripheral retina—everything from normal anatomy, including the pars plana, ora serrata and the retinal veins, to retinal holes, retinal tufts (*Figure 1, page 30*), retinal detachments and retinoschisis.

Here, I will review the types of pathology and features that one can find in the peripheral retina, focusing on three different types of retinal pathology—retinal hole, typical cystoid degeneration and typical degenerative senile retinoschisis—

Take-Home Point

Ultra-widefield spectral-domain optical coherence tomography can image the eye out to 200 degrees or more beyond the level of the pars plana. This article reports on a study that documented 19 different types of features in the peripheral retina that were previously not viewable with conventional OCT technology.

ABOUT THE AUTHORS

Dr. Choudhry is on faculty at the University of Toronto and practices at the Herzig and Prism Eye Institutes in the greater Toronto area.

Mr. Golding is the vitreoretinal diagnostic imaging specialist at Herzig Eye Institute, Toronto.

DISCLOSURES: Dr. Choudhry disclosed relationships with Optos Plc. and Topcon Corp. Mr. Golding is a consultant to Optos and Topcon.

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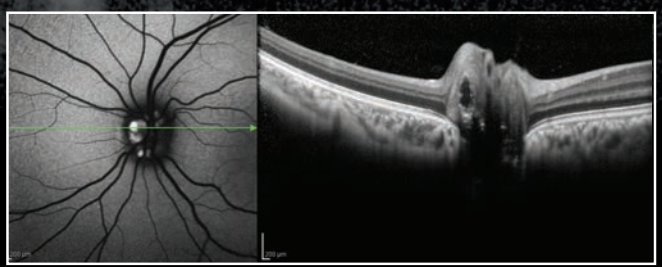

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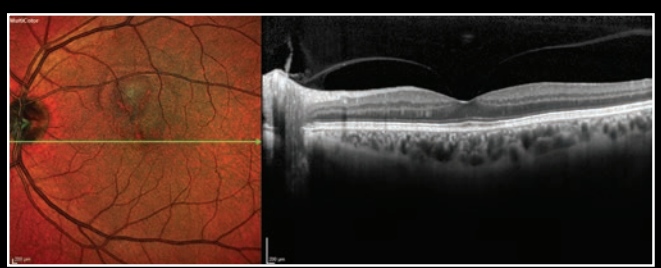

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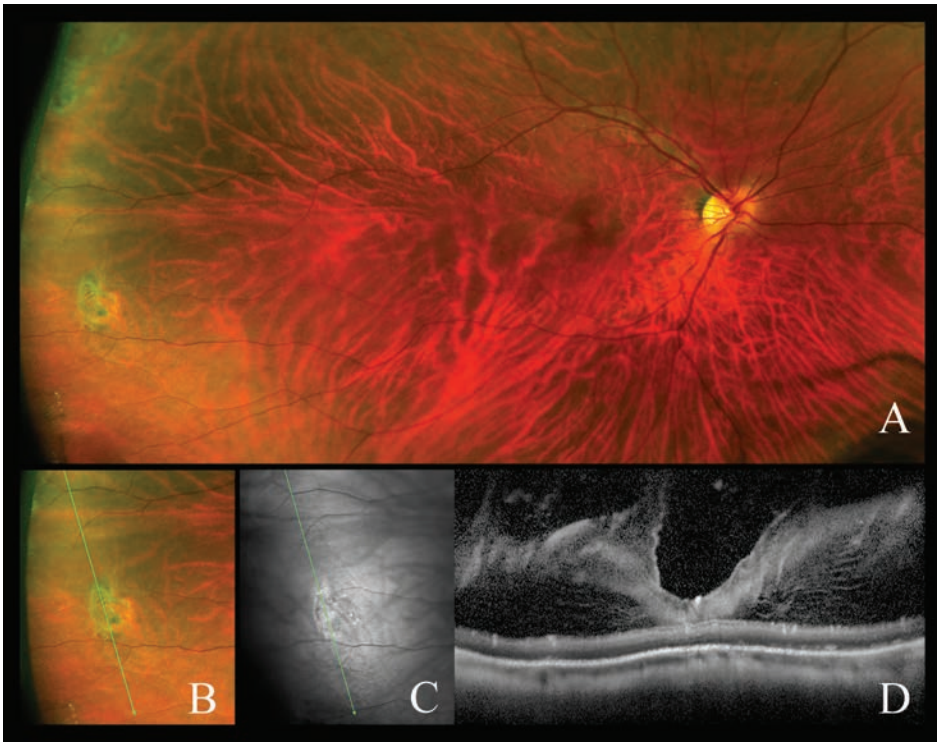

Figure 1. Ultra-widefield pseudocolor image (A) of the right eye demonstrates a retinal tuft, with a high-magnification view (B). Near-infrared reflectance image (C) of a retinal tuft. Spectral-domain optical coherence tomography (D) demonstrates concave vitreous adhesion at the retinal interface of the retinal tuft, while the underlying retinal layers appear normal.

19 Peripheral Retinal Features Seen with UWF SD-OCT

1. Vortex vein
2. Congenital hypertrophy of the retinal pigment epithelium
3. Pars plana
4. Ora serrata pearl
5. Typical cystoid degeneration
6. Cystic retinal tuft
7. Meridional fold
8. Lattice degeneration

a 30-degree, off-the-shelf lens that comes with the Heidelberg Spectralis SD-OCT device. This study involved an experienced retinal photographer operating a single commercially available SD-OCT device (Heidelberg). This approach registered near-infrared scanning laser ophthalmoscopy images and SD OCT of these entities to UWF color photographs.

Having a skilled retinal photographer is integral in obtaining quality images of the outer retina. Image capture requires significant interplay between photographer and patient, and the process can take five to seven minutes with very compliant patient and skilled photographer. Montaging the images can take 15 to 20 minutes.

To maximize dilation in patients, we administered three sets of standard drops of phenylephrine and tropicamide, and we used an approach similar to what our group previously developed for viewing the seven standard fields for diabetic retinopathy.[4]

This approach enabled us to direct, or steer, the OCT laser head out to the periphery and obtain high-quality, reproducible SD-OCT images of peripheral retina findings and register the near-infrared reflective images to their Optos 200-degree UWF images. We also used this approach to obtain a continuous, near 200-degree SD-OCT montage from one side of the retinal periphery to the other.

When talking about OCT, "wide-field" typically means obtaining an SD-OCT image with a 50-degree field of view. UWF, on the other hand, describes capturing a 200-degree field of view in a single image.[5–8] In evaluating the retinal periphery, retina specialists have relied upon en-face UWF-based fundus fluorescein angiography and autofluorescence, mostly for imaging vascular diseases. However, this modality does not provide cross-sectional imaging.

Features In The Periphery

Using UWF SD-OCT in the 68 study patients, we were able to identify the following features in the peripheral retina.

Retinal hole. UWF SD-OCT identified 17 retinal holes, all of which revealed subretinal fluid within the hole and the operculum, either attached, partially attached or completely detached (*Figure 2*). In the retinal holes with a partially attached operculum, we could see vitreous hyper-reflectivity attached to the inner retina, but no such adhesions were visible in adjacent cross sections.

9. Cobblestone degeneration
10. Retinal hole
11. Retinal tear
12. Rhegmatogenous retinal detachment
13. Typical degenerative senile retinoschisis
14. Peripheral laser coagulation scars
15. Ora tooth
16. Cryopexy scars (retinal tear and treated retinoblastoma scar)
17. Bone spicules
18. White without pressure
19. Peripheral drusen

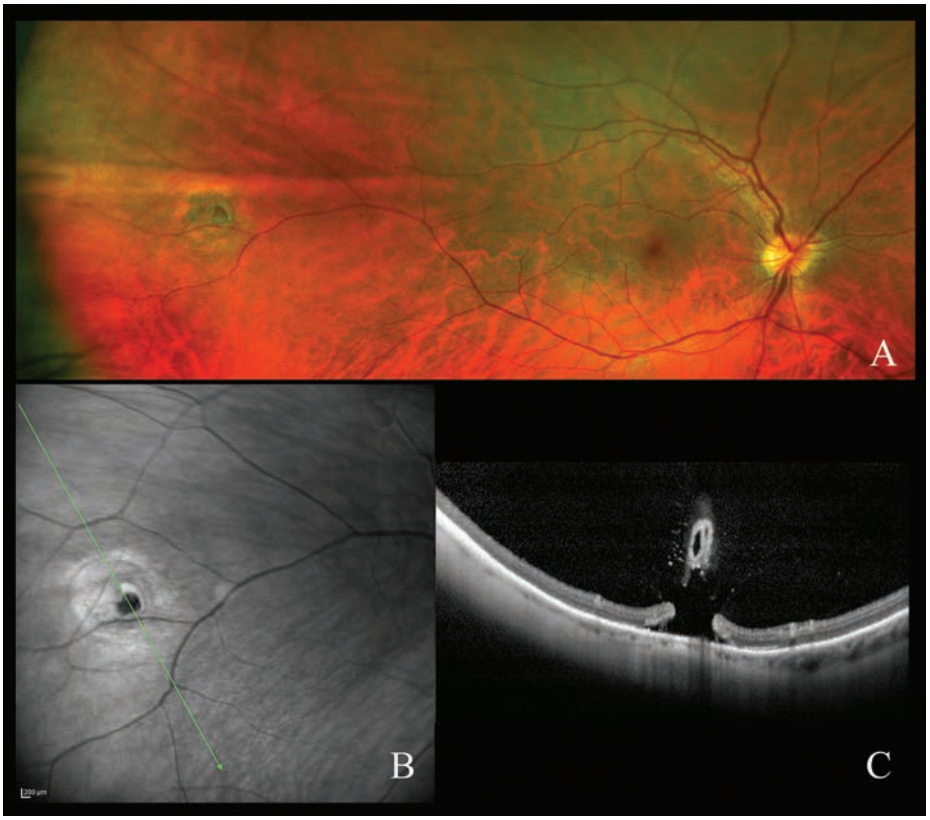

Figure 2. Ultra-widefield pseudocolor image (A) of the right eye demonstrates an operculated retinal hole. Near-infrared reflectance image (B) of a retinal hole. SD-OCT (C) demonstrates an open retinal hole with a free-floating operculum. Subretinal fluid can be seen at the base of the open the retinal hole.

In the retina surrounding the hole, we visualized variable regions of cystoid degeneration with hyper-reflectivity of the subretinal space. When we examined the configuration of the retinal holes more closely, we identified two distinct shapes characteristic of pathology: a V-shape was consistently characteristic of an attached or partially attached operculum; whereas a flat shape was typical of no attached vitreous hyper-reflectivity or subretinal fluid.

Typical cystoid degeneration. UWF color and near-infrared scanning laser ophthalmoscopy and peripheral SD-OCT provided imaging of typical cystoid degeneration (TCD) in six eyes (*Figure 3, page 32*). On SD-OCT, hyporeflective cystoid cavities and columns created a saw-tooth pattern that defined the area of TCD. Many of these cavities and columns spanned the entire thickness of the neural retina.

The pars plana epithelium secretes the mucopolysaccharide of the vitreous, and, when imaged, the condensed cortical vitreous appears as a moderately reflective layer above the pars plana and peripheral retina structures. We could also see the ora serrata pearl, which has not been previously imaged. At the apex of the raised surface of the ora serrata pearl, we could also see vitreous adhesion to the inner retina.

Retinoschisis. We created a continuous UFW montage of an eye with typical degenerative senile retinoschisis, giving us coverage of high-resolution retinal and choroidal features in a single 200-degree image that was not available previously. This involved serial SD-OCTs from periphery to periphery, through the fovea and optic nerve and to the retinoschisis. The montaged image showed schisis of the inner nuclear and outer plexiform layers of the retina posteriorly in the temporal macula that extended into the periphery. The degree of intraretinal splitting widened progressively from the posterior to anterior retina. We also used peripheral SD-OCT to analyze an inferotemporal portion of the retina, revealing schitic splitting along the inner nuclear and outer plexiform layers.

The Potential of UWF SD-OCT

We have shown that UWF SD-OCT is a reproducible technique that can achieve high-quality images with a high level of retinal anatomy and vitreous detail, and in many cases great choroidal detail. The ability to assemble mon-

Quotable

UWF SD-OCT also has great potential for use in telemedicine. This approach can improve the ability of retina specialists to treat and manage peripheral retinal pathologies via telemedicine in underserved areas.

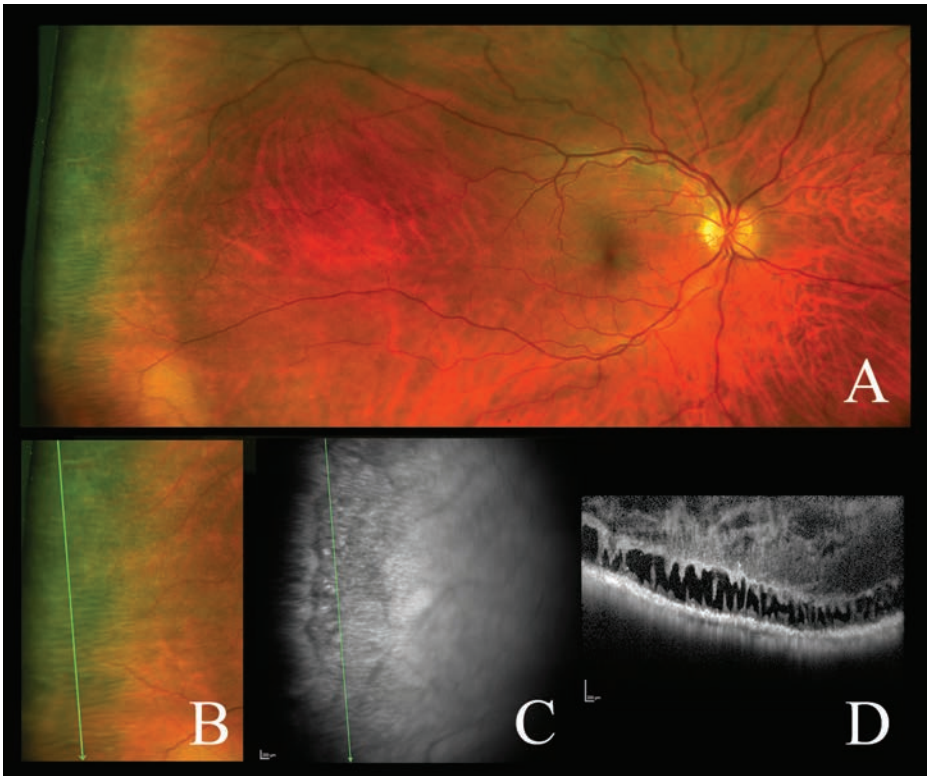

Figure 3. Ultra-widefield pseudocolor image (A) of the right eye demonstrates a peripheral cystoid degeneration, with high-magnification view (B) and a near-Infrared reflectance image (C) of the same. SD-OCT of peripheral cystoid degeneration (D) demonstrates a "saw-tooth" schisis-like separation of the retinal layers. The retinal layers are not distinguishable by their usual laminar orientation. The underlying retinal pigment epithelium appears irregular and the overlying vitreous (formed) is distinct and attached to the inner retina.

taged images can provide a "bird's-eye" view of the retinal periphery. This may give us a greater understanding of the association between pathology in the retinal periphery and the macula.

What's more, comparing dynamic, cross-sectional images of the retinal periphery over time could improve our understanding of not only cystic retinal tufts, lattice degeneration, retinal holes and retinoschisis with inner and outer layer holes, but even tumors, meridional folds and previously treated or spontaneously scarred retinal tears. Furthermore, SD-OCT with UWF color imaging can allow us to visualize changes in subretinal fluid over time, improving our ability to study the course of these entities and estimate the risk of these findings progressing toward vision impairment.

UWF SD-OCT also has great potential for use in telemedicine. This approach can improve the ability of retina specialists to treat and manage peripheral retinal pathologies via telemedicine in underserved areas. We expect to see a prototype of UWF SD-OCT in the next two years.

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DIABETES DRUGS IN THE RETINA PRACTICE

How glucose-lowering therapies can influence surgical planning.

By Peter J. Lin, MD, CCFP

Currently there are 422 million people with diabetes in the world,[1] and if they all lived in one country, that would be the third largest country in the world, even beating out the United States. A disproportionately large number of retina patients have diabetes, so it is important for retina specialists to know about the new treatments for diabetes and potential issues that they may encounter. This article is not meant to be an exhaustive review, but more to highlight key features of the most common classes of diabetes drugs.

Insulin

There are three basic types of insulins: long-acting; short-acting; and premixed, which combines short- and long-acting insulins. Long-acting insulin is taken often at night, while short-acting insulins are used to deal with meals. Premixed insulin aims to simplify dosing by having both types of insulin in one shot.

For a surgeon, the greatest worry with insulin is the risk of hypoglycemia. For example, if the diabetes patient ordered to take nothing by mouth for surgery takes the usual insulin dose, then the glucose can become too low and he or she may even pass out. Some patients do the opposite and stop all of their insulin because they're not eating anything, so they think they don't need insulin. In these cases, they will not have insulin to move glucose into the cell for energy production, which can trigger diabetic ketoacidosis (DKA).

Perhaps the best strategy is to have patients get instructions from their endocrinologist on the proper dosing of insulin for surgery. Also, make sure the dosing is documented; hopefully, this will minimize the risk of both hypoglycemia and DKA.

Biguanide (Metformin)

Normally, the liver supplies glucose when we are not eating; that keeps us alive as we sleep. But in diabetes, the liver produces too much glucose. Biguanides work by slowing down this process, thereby lowering glucose. Metformin is the only available biguanide.

Metformin does not cause hypoglycemia, but at higher dosages it can cause diarrhea. Metformin is also cleared through the kidneys. If renal function declines, then metformin can accumulate, and this could lead to lactic acidosis. So if the estimated glomerular filtration rate (eGFR) is less than 60, then the patient needs to reduce the metformin dosage; and if the eGFR goes below 30, the patient should stop metformin.

ABOUT THE AUTHOR

Dr. Lin is director of primary care initiatives at the Canadian Heart Research Centre in North York, Ontario.

DISCLOSURE: Dr. Lin is associate editor of Elsevier Web-Portal PracticeUpdate Primary Care and medical director of LinCorp Medical Inc.

Diabetes Medications

Biguanides

Biguanides slow glucose production in the liver to lower glucose.

- Metformin

Sulphonylureas

Sulphonylureas cause the pancreas to increase production of insulin to lower glucose levels.

- Glyburide/Glibenclamide
- Glipizide
- Gliclazide
- Glimepiride

-glucosidase inhibitors

α-glucosidase inhibitors block the α-glucosidase enzyme in the intestine to control blood-glucose levels.

- Acarbose
- Miglitol

Thiazolidinediones

Thiazolidinediones activate insulin to lower glucose levels.

- Rosiglitazone
- Pioglitazone

GLP-1 Receptor Agonists

GLP-1 receptor agonists act on the glucagon-like peptide 1 in the small intestines to reduce glucose.

- Exenatide
- Exenatide extended release
- Liraglutide
- Albiglutide
- Lixisenatide
- Dulaglutide

DPP-4 Inhibitors

These agents inhibit the dipeptidyl peptidase-4 to block the breakdown of GLP-1 to reduce glucose levels.

- Sitagliptin
- Vildagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

SGLT2 Inhibitors

These drugs inhibit the subtype 2 sodium-glucose transporter protein from producing glucose.

- Canagliflozin
- Dapagliflozin
- Empagliflozin

The concern for surgeons with patients on metformin is dehydration perioperatively. The dehydration could worsen renal function enough that the metformin accumulates, which could then lead to lactic acidosis. Contrast dyes for imaging can also worsen renal function. Radiology will often ask for the creatinine and eGFR levels before using contrast dyes in patients with diabetes. So for elderly patients on metformin, it is important to have a recent creatinine and eGFR on file for reference.

Sulphonylureas

There are several molecules in the sulphonylurea category: glyburide/glibenclamide, glipizide and glimepiride. Sulphonylureas make the beta cells in the pancreas secrete more insulin, which then lowers glucose levels. They are inexpensive, and the glucose drop is rapid and satisfying.

Unfortunately, these medications continue to push out insulin even when glucose levels are low. Clinical trials have shown hypoglycemia occurring in up to 40 percent of patients using these medications. Also, because the pancreas works so hard, eventually it loses its ability to secrete insulin, requiring additional medications.

Sulphonylureas may increase the risk of hypoglycemia when patients are NPO before surgery, so their glucose levels need to be monitored. Also, sulphonylureas are cleared through the kidneys, so dehydration and worsening of renal function could lead to an accumulation of these medications, which could also cause hypoglycemia.

Take-Home Point

Patients with diabetes have a multitude of medications they can take, many in combination, to manage their blood-glucose levels, but these drugs can have variable effects when patients take, modify or stop their dosing around the time of surgery. Therefore, retina specialists need to be aware of the potential complications diabetes drugs can cause and consult with their endocrinologist or treating physician when planning surgery ocular surgery in patients with diabetes.

α-glucosidase Inhibitors

Acarbose and miglitol block the α-glucosidase enzyme in the intestine, which normally breaks down starch into individual glucose molecules so that the gut can absorb them. Without that breakdown, the body could not absorb glucose. Bacteria in the colon eventually processes undigested starches, which unfortunately produces gas, hence the main side effect of this class of medication—flatulence.

α-glucosidase inhibitors do not cause hypoglycemia on their own, but they are often used with other medications that can cause hypoglycemia.

The key issue, though, with this class of medication is that when patients taking them become hypoglycemic, the usual treatments do not work. For example, normal table sugar will not work because the enzyme is blocked and they cannot break down the sugar into single molecules.

These patients would need pure glucose tablets instead to treat the hypoglycemia. So for patients on alpha-glucosidase inhibitors, glucose tablets should be available in the office to treat their hypoglycemia appropriately.

Thiazolidinediones

Thiazolidinediones (TZDs) include pioglitazone and rosiglitazone. As insulin sensitizers, TZDs make insulin work better.

Rosiglitazone was implicated in causing myocardial infarctions and death, although this was later dispelled.

TZDs can cause weight gain and edema, and have been associated with heart failure and bone fractures. They do not cause hypoglycemia on their own.

GLP-1 Receptor Agonists

GLP-1, which stands for glucagon-like peptide, is a hormone the small intestine releases when we eat. The bloodstream transports GLP-1 to the pancreas and signals the beta cells to produce insulin because food is on the way. GLP-1 also signals alpha cells in the pancreas to stop making glucagon, the hormone that puts glucose into the bloodstream when we are not eating. Obviously with food coming in, there is no need for glucagon production. So when you eat, GLP-1 turns on insulin and turns off glucagon.

However, in patients with type 2 diabetes, GLP-1 does not activate fast enough after meals, and they also do not make enough GLP-1 compared to patients without diabetes. This GLP-1 deficiency means that insulin levels do not increase properly and the glucagon does not decrease properly. This combination results in higher glucose levels.

The discovery of reduced GLP-1 in patients with type 2 diabetes led to the concept of restoring GLP-1 back toward normal levels. But GLP-1 is a large-protein hormone so it has to be injected into the body. In normal humans, the DPP-4 enzyme (for dipeptidyl peptidase) inactivates GLP-1 in two minutes. Hence, scientists looked for analogs of GLP-1 that appeared similar, but were different enough that they would not break down so fast.

Exenitide was found in the saliva of the gila monster lizard.[2] It has about 50 percent of the same amino acid sequence as human GLP-1, so it does not break down too quickly and can be given twice a day. Liraglutide was created by adding amino acids to human GLP-1,[3] and it can be given once a day. Once-weekly formulations are now available as well.

These agents do not cause hypoglycemia, but they do cause nausea, especially when patients first take them as they titrate the medicine upward. This is important to know after eye surgery because nausea and vomiting may increase intraocular pressures. Ideally, patients should not start these GLP-1 agents pre- or postoperatively. An association with pancreatitis has been reported, so patients with a history of pancreatitis should not take them.

DPP-4 Inhibitors

DPP-4 normally breaks down GLP-1, but levels of GLP-1 are already too low in patients with type 2 diabetes. Hence, a DPP-4 inhibitor slows the breakdown of GLP-1, allowing for more GLP-1 to be present and to do its job properly.

DPP-4 inhibitors are not large proteins, so patients can take them orally as a pill. They do not cause hypoglycemia and are cleared through the kidneys, so dosing needs to be lowered with lower eGFRs.

DPP-4 inhibitors were initially associated with pancreatitis, so avoiding them in patients with a history of pancreatitis is recommended. Many of these DPP-4 inhibitors have been combined with metformin into a single tablet. This means that all the precautions that were mentioned about metformin would apply to these DPP-4 inhibitors/metformin combination therapies as well.

SGLT2 Inhibitors

Glucose is a small molecule, so in the kidneys it will leak out into the urine. But glucose is the body's fuel source and SGLT (sodium-glucose transporter protein) acts as a pump that pulls the glucose from the urine back into the bloodstream after it

filters out. In patients with diabetes, a large amount of glucose ends up in the urine. SGLT senses all this wasted energy and works hard to pull it back. This overactive SGLT pump, unfortunately, keeps the blood glucose levels very high.

So one way to lower glucose would be to block these SGLT pumps and let the glucose leave the body in the urine. The SGLT1 pumps about 10 percent of the glucose back, while SGLT2 pumps handle about 90 percent. So SGLT2 inhibitors were made to give maximum blocking of the glucose pump.

SGLT2 inhibitors do not cause hypoglycemia, but they do cause water and salt loss along with glucose into the urine, so they are like mild diuretics. This means that at the time of surgery, patients can get more dehydrated from these medications. DKA has been reported in patients using insulin with SGLT2 inhibitors when they get dehydrated or stop their insulin.

Call the Endocrinologist

For advice on these medications around the time of surgery, consult with patients' endocrinologists or treating physician about appropriate dosing of insulin and all their other diabetes medications. The typical strategy is to have patients stop or reduce these medications around the time of surgery and then restart them afterward.

Patients with diabetes will become the largest single group any health-care provider sees. The worry with patients who have diabetes is the risk of hypoglycemia and dehydration around the time of surgery. We all need to stay informed about their treatments and any precautions we need to take.

The number of patients with diabetes will continue to grow, as will the number of medications that they take. Our job is to make sure that we get the best out of these medications while we minimize the harm.

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Will OCT Angiography Replace FA?

(Continued from page 27)

of OCTA and resolve its susceptibility to motion artifact, making OCTA a formidable challenger to FA, or even the champion for imaging posterior pole disorders.

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STEM CELLS FOR RETINA: WHERE ARE WE NOW?

A review of multiple trials pursuing a breakthrough in cell-based therapies for AMD and hereditary retinal disorders.

By Vaidehi S. Dedania, MD, and Rajesh C. Rao, MD

Cell death in degenerative retinal diseases like non-exudative age-related macular degeneration and glaucoma, as well as hereditary degenerations, poses a unique structural and functional dilemma. The absence of cells, and resident stem cells that can reconstitute these differentiated cell types, precludes gene therapy and many pharmacologic treatments. Stem cell therapy has been proposed as a means to replace the lost cells.

In degenerative retinal diseases, particular cell types die. These include retinal ganglion cells (RGCs), retinal photoreceptors (PRs) and retinal pigment epithelium (RPE) cells, and they do not appreciably regenerate to restore lost function. Stem cells are an attractive source of cell therapy. They harbor the key ability to self-renew (i.e., make more copies of themselves) and differentiate (i.e., form into specialized cell types like RPE).[1] In this way stem cells can generate clinically relevant amounts of the cell types lost in disease.

Progenitor cells are similar to stem cells; however, their ability to self-renew or differentiate into multiple cell types is more limited. Stem cell therapy is classically considered to be one type of cell therapy, in which clinicians use stem/progenitor cells to produce differentiated cells such as RGCs, PRs and RPE *in vitro* or *in vivo*. However, many stem cells also produce a multitude of proteins (also called cytokines), some of which promote the survival of dying RPE and PR cells that are dysfunctional but still alive in AMD. This could theoretically slow the progression of retinal degeneration, even if the stem cells do not replace the dying cells or restore function.[2]

Here, we review the types of stem cells used for treatment of retinal diseases and the findings of some past studies, and we explore the early results and safety concerns related to this technology.

Types of Stem Cells

Cell therapy uses three classes of stem/progenitor cells: pluripotent stem cells (PSCs); fetal cells; and

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DISCLOSURE: The authors have no conflicts to disclose.

postnatal/adult cells (*Figure 1, page 40*).

Many cell-based therapies for retinal diseases use PSCs, which can form in any tissue of the body. Because they can self-renew indefinitely, PSCs could generate nearly unlimited amounts of differentiated retinal tissues.[1] The most common stem cells currently employed for the treatment of retinal diseases are two types of PSCs—human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs)[3]—and a non-pluripotent cell type, so-called "adult" stem cells.

Embryonic stem cells are pluripotent and are cultivated from the inner cell mass of a five-day-old blastocyst,[1] while iPSCs are PSCs derived from reprogrammed differentiated somatic cells, such as adult skin fibroblasts (connective tissue near the skin) or white blood cells.[3] These hESCs and iPSCs can then be converted to neural retinal or RPE cells.

Other classes of stem/progenitor cells that have been used in trials for retinal diseases are derived from the fetal central nervous system—the developing brain, spinal cord and retina.[4] Fetal retinal stem/progenitor cells build the retina during embryonic development through limited self-renewal and tissue-specific differentiation.[5]

So-called "adult stem cells" are post-natal cells that can generate some, or all, of the cell types of the organs from which they originate. For instance, hematopoietic stem cells are derived from bone marrow and can reconstitute all the cells of the blood (red and white cells, platelets, etc.), and are used in patients with blood cancers or immunodeficiencies.[6] In fact, hematopoietic cell transplantation is currently the only Food and Drug Administration-approved cell therapy.[6,7]

Various clinical trials have proposed bone-marrow-derived cells, such as various subpopulations of blood cells, umbilical tissue-derived cells, mesenchymal stem cells and adipose (fat) cells, for a variety of retinal disorders.[8]

Bone Marrow Cell Therapy

The "Holy Grail" of stem cell therapies is the replacement of dead or dying retinal cells with stem-cell-derived cells to restore vision. Indeed, in bone marrow transplantation, cells produced from donor bone marrow partially replace the recipients' blood system, leading to restoration of the immune system and other functions fundamental to the hematopoietic system, like oxygenation.

However, in the human central nervous system, which includes RGCs, there is little evidence that stem cells or stem-cell-derived cells can themselves produce the missing or dying cell types following transplantation. One exception is PSC-derived RPE; early phase clinical trials have shown patches of increasing pigmentation after transplantation of donor-derived RPE into the subretinal space.[9] Still, to date there is no evidence that stem-cell-derived cells, such as RPE, can improve or restore vision. Further study and larger, prospective trials will be needed.

If stem cells or stem-cell-derived cells cannot produce the missing cell types and integrate into the host retina to restore function, why consider stem cells as a route to therapy? Stem cells, like other cells, are cytokine-producing factories. These cells secrete growth factors that may improve the survival and function of host cells.[2] Thus, salutary effects of cell therapies, such as stem-cell transplantation in the human retina, may be secondary to this indirect effect, rather than direct replacement of dying retinal cells with those derived from stem cells.

There are three methods for delivering stem cells (*Figure 2, page 42*).

To date, only results of early phase stem/progenitor cell therapy trials have been reported. In general, most trials were Phase I or IIA, and not powered to detect efficacy. The primary goal of these trials has been to determine whether these interventions are safe. It is important to note that none of these trials included control groups, although they did monitor untreated fellow eyes.

PSC-based Trials

Several PSC-based trials are in progress. Ocata Therapeutics, acquired earlier this year by Astellas Pharma, was among the first to conduct PSC-based trials in humans. These include Phase I/II trials of human ESC-derived RPE for dry AMD, Stargardt disease and myopic macular degeneration in the United

Take-Home Point

While no Food and Drug Administration-approved cell or stem cell treatments currently exist for retinal disease, stem and progenitor cells have the ability to self-renew and specialize into another cell type. Three classes of stem/progenitor cells are used in therapy: pluripotent stem cells (PSCs); fetal stem cells; and postnatal/adult cells. PSC-based retinal pigment epithelium trials are the only interventions that have resulted in replacement of dying or missing cell types. Although no trials have yet reported statistically significant improvements in vision or visual function, some stem/progenitor cell-based therapies appear feasible despite adverse events that have occurred in trials, which include endophthalmitis, retinal detachment and proliferative vitreoretinopathy.

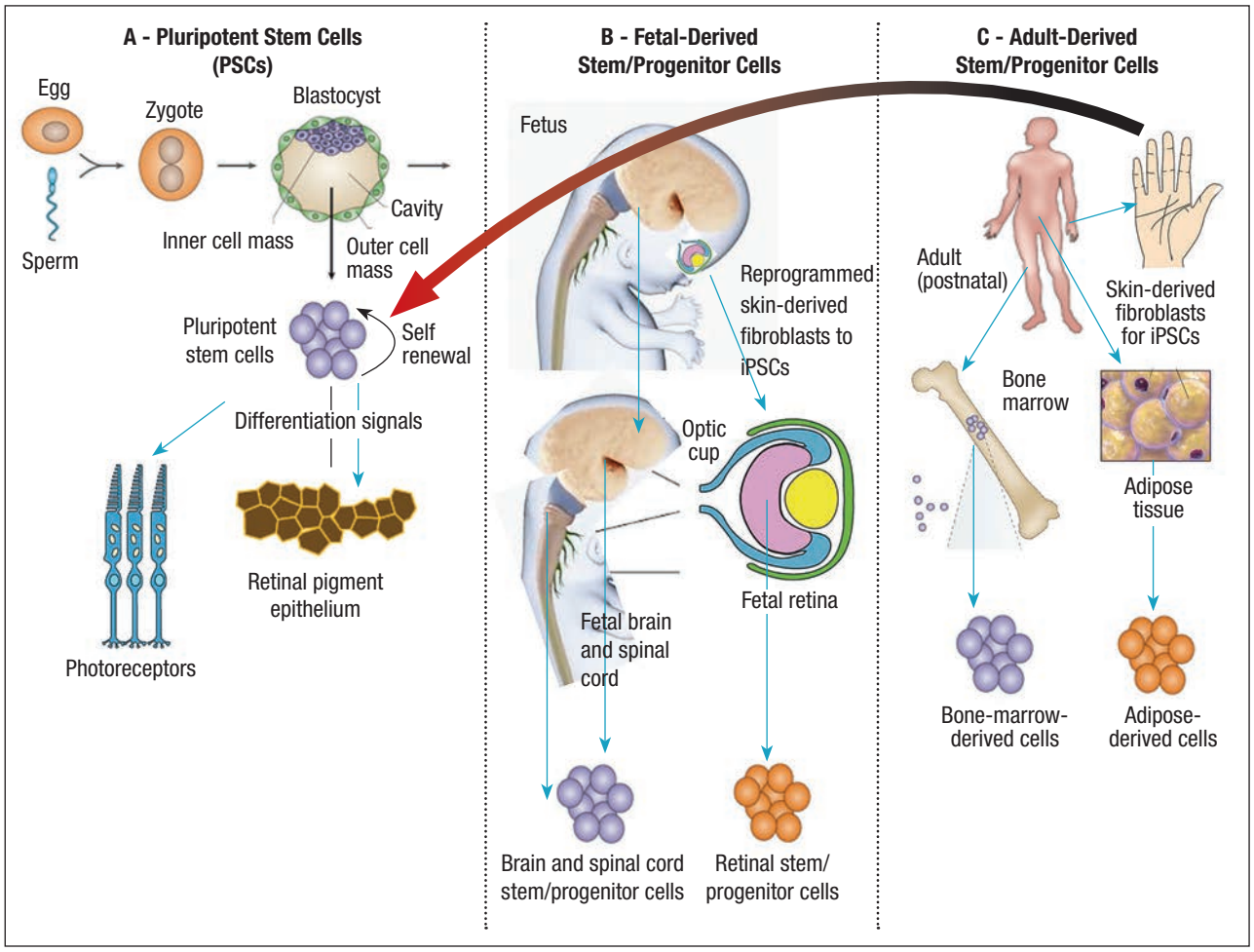

Figure 1. Cell therapy uses three classes of stem/progenitor cells: pluripotent stem cells (PSCs); fetal cells; and postnatal/adult cells. PSCs (A) are derived from the inner cell mass of blastocysts (five-day-old embryos) or from reprogrammed skin cells (arrow from C). They can be differentiated to photoreceptors (not yet used in clinical trials) and retinal pigment epithelium (currently in use in clinical trials). Fetal stem/progenitor cells (B) are derived from the fetal central nervous system, such as the developing brain, spinal cord and retina.[4] A few clinical trials have used fetal retinal stem/progenitor cells, which "build" the retina during embryonic development.[5] In many cases, these cells do not actually replace dying retinal cells, but could indirectly support survival of host retinal cells through secretion of pro-survival proteins known as cytokines. Adult stem cells (C) can generate some, or all, of the cell types of the organs from which they are harvested. Various clinical trials have proposed use of bone-marrow-derived cells for a variety of retinal disorders.[8] In these cases, these cells do not actually replace dying retinal cells, but could indirectly support survival of host retinal cells through secretion of pro-survival cytokines.

States, United Kingdom and Korea. A recent report detailing two trials that used systemic immunosuppression (tacrolimus and mycophenolate mofetil) in combination with subretinal transplantation in human ESC-derived RPE for dry AMD (nine patients) and Stargardt disease (nine patients), showed increased subretinal pigmentation at the border of atrophic lesions, consistent with subretinal RPE transplantation, in 13 of 18 patients.[9] The median follow-up was 22 months.

In the 18 studied eyes, best-corrected visual acuity improved in 10 eyes, remained the same in seven eyes and decreased by more than 10 letters in one eye. Untreated fellow eyes did not have similar improvements in visual acuity. Consistent with findings from pre-clinical studies, these authors reported no correlation between increased subretinal pigmentation and improvement in vision.[9] Importantly, while these trials suggest a biologic effect, larger

studies are needed to detect a true effect.

Local adverse events included cataract progression, and separate, single cases of focal RPE loss at the injection site, epiretinal membrane and vitreous inflammation with intravitreal membrane formation and *Staphylococcus epidermidis* endophthalmitis that resolved two months after intravitreal antibiotic therapy.[9]

Other serious adverse events included hemiparesis, chest pain, femoral neck fracture, mental status change and skin cancers, some of which may have been unrelated to the treatment or due to systemic immunosuppression.[9] Importantly, these trials did not detect any tumor formation. A Korean study recently reported similar results in four patients (two with dry AMD and two with Stargardt disease).[10]

The first ever iPSC-based intervention to be tested in humans is a recent trial for wet AMD, at the RIKEN Institute in Japan. In September 2014, researchers injected autologous iPSC-derived RPE subretinally into a woman with wet AMD.[11] The patient had previous anti-VEGF injections, and the procedure the authors described involved resection of subretinal fibrotic tissue prior to subretinal injection of the cells. The autologous iPSCs were originally derived from the patient's own skin fibroblasts. Short-term safety data suggested that the procedure was safe.

However, on reprogramming skin fibroblasts to iPSCs in the second patient, the authors detected genomic alterations (mutations and copy number variations) not present in the original cells. Theoretically, such mutations could increase the risk of tumor growth from the iPSC-RPE cell. In response, the RIKEN Institute halted the autologous iPSC-RPE trial in 2015.[12] As of June 2016, the investigators planned to resume the trial, but they will no longer use autologous cells derived from the patient's own skin, reprogrammed to iPSCs, differentiated to RPE and then transplanted into the same patient. Instead, banked, allogeneic iPSCs will replace the autologous iPSCs as the source for RPE.[13]

Other studies, such as a trial sponsored by Pfizer, will attempt to grow PSC-derived RPE on a scaffold and then transplant the RPE-scaffold subretinally.

Fetal Stem/Progenitor Cells

While no studies of fetal-derived stem/progenitor cell therapies have been published, abstracts have described the subretinal transplantation of human fetal spinal cord and brain-derived central nervous stem cells (HuCNS-SCs) in geographic atrophy in a 15-patient, open-label Phase I/II study.[4] A prospective analysis showed an increase in subfield thickness and macular volume in the treated eye vs. the untreated eye, as well as slowed growth of geographic atrophy. However, a reading center's post-hoc analysis did not confirm the latter findings. Few details on adverse events are available, and with the dissolution of the company sponsor, Stem Cells Inc., it remains to be seen whether development of this technology will continue.

Importantly, the investigators have made no claim that the HuCNS-SCs actually differentiate to RPE or photoreceptors, but instead may slow GA indirectly through secretion of cytokines that promote survival of the recipient's RPE.

Massachusetts Eye and Ear and Harvard Medical School recently initiated a fetal retinal progenitor cell transplant trial. Unlike the PSC-based trials, and similar to the brain/spinal cord fetal neural stem cell trials, the cells are not differentiated to mature cells such as RPE or photoreceptors; rather, they are injected as precursor cells.[15] This work involves subretinal transplantation of fetal retinal progenitor cells in a study sponsored by ReNeuron Group as part of a Phase I/II trial for advanced retinitis pigmentosa. Clinical and safety data are not yet available. The company and study investigators hope to see that the fetal retinal progenitor cells improve vision by directly differentiating to photoreceptors or by an indirect effect: secretion of factors that promote survival of host retinal cells.

Another company, jCyte, is slated to begin its first fetal retinal progenitor cell transplants through intravitreal injections. The rationale is that the fetal retinal progenitor cells will clump in the vitreous and secrete factors that will slow retinitis pigmentosa rather than migrate to the retina and differentiate to mature retinal cells.[16]

It is important to note that the rationale in all of these fetal stem/progenitor retinal transplant trials is not necessarily to replace dying RPE and photoreceptors with stem cell-derived RPE and photoreceptors. Instead, any actual biological effect would likely be an indirect one, perhaps through the secretion of cytokines to promote survival of the recipients' own retinal cells. This approach stands in contrast to PSC-based RPE trials in which the goal has been to actually replace the dying or dead RPE with PSC-derived RPE and restore vision.

'Adult' Stem/Progenitor Cells

By far the most common "stem cell" trials for retinal diseases are sourced from often heterogeneous cell populations known as "adult"

stem/progenitor cells—postnatal cells isolated from the individual sometime after birth.

For instance, the umbilical-tissue-derived cells used in Centocor Inc.'s trial are isolated from umbilical tissue present immediately after birth. Other cell types such as adipose/fat tissue are typically isolated from an adult patient. Umbilical tissue, fat, white blood cells and many other cell types used in these trials are ultimately bone-marrow-derived.

The rationale of using bone-marrow-derived cell transplants for retinal disease is not well understood, but preclinical models have suggested that these cells secrete cytokines that might preserve retinal cells through actions on the cells themselves and/or by stabilizing retinal vessels.[17] It is important to keep in mind that the traditional animal model for proliferative vitreoretinopathy (PVR) is to inject bone-marrow-derived cells (plasma) into the vitreous.[18] Therefore, some of the adverse events reported in some of the trials we review here appear to be consistent with the interventions known to produce to PVR in animal models.

These bone-marrow-derived adult stem/progenitor cell types do not generate retinal tissues. Therefore, unlike PSC-based trials but similar to fetal stem/progenitor-cell-based trials, the potential biological effect from adult stem/progenitor trials would be due to cytokine release that promotes retinal cell survival, rather than directly replacing dying or dead RPE or photoreceptors.

Bone-Marrow-Derived Cells

More than 10 bone-marrow-derived cell therapy trials for retinal diseases are currently listed at clinicaltrials.gov, but here we will review only some of these trials based on the availability of published reports.

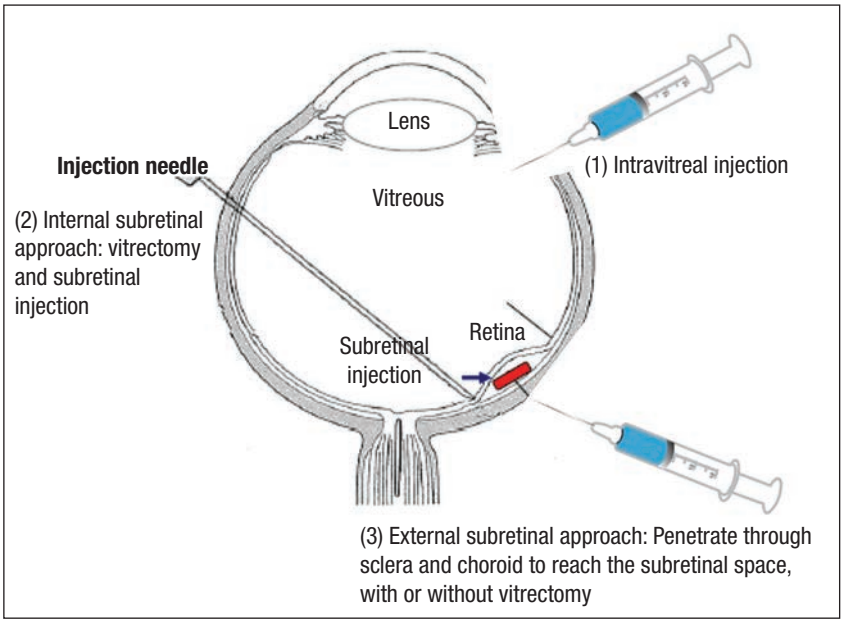

Figure 2. Investigators have employed three methods of intraocular delivery of cell therapies: intravitreal; internal subretinal; and external subretinal. The internal subretinal approach accesses the subretinal space intraocularly (usually after vitrectomy) while the external subretinal approach accesses the subretinal space via the choroid and sclera.

Investigators at the University of California, Davis, reported on six-month data of six eyes in a trial involving intravitreal injection of the CD34+ fraction of autologous bone-marrow-derived cells for retinal vascular occlusion, dry AMD or retinitis pigmentosa.[19] There was no visual benefit, no improvement and no worsening of the electroretinogram (full-field and multifocal), and the cells were linked to hyper-reflective macular deposits on adaptive optics optical coherence tomography in one patient. The authors reported no adverse local or systemic side effects.[19]

Another trial, by MD Stem Cells, involved intravitreal, retrobulbar, sub-Tenon's, subretinal and intra-optic nerve injections of autologous bone-marrow-aspirate-derived cells for "glaucoma, ischemic optic neuropathy, optic atrophy, optic neuritis and some trauma." The so-called Stem Cells Ophthalmology Treatment Study (SCOTS) is self-described as "the largest ophthalmology stem-cell study registered at the National Institutes of Health to date." In a June 2015 case report, SCOTS investigators reported marked bilateral vision improvements in one woman with idiopathic optic neuritis who received intravitreal injections of bone-marrow-derived cells.[20] The authors reported no adverse events in this patient apart from "tearing and conjunctival ecchymosis."

A few months later, SCOTS investigators reported marked bilateral improvements in vision in a woman with relapsing optic neuritis who received vitrectomy with injection of autologous bone-marrow-derived cells into the optic nerve of the right eye, and retrobulbar, sub-Tenon's and intravitreal injections of the same in the left

eye.[21] A June 2016 case report by non-SCOTS investigators described their findings and intervention in a man with a history of Stargardt disease who developed proliferative vitreoretinopathy with a recurrent retinal detachment following treatment in the SCOTS trial.[22]

The patient originally underwent a pars plana vitrectomy and subretinal injection of autologous bone marrow-derived cells in the right eye at another facility. A month later, he underwent an intravitreal injection of similar cells in the left eye. He developed a retinal detachment and was treated with a scleral buckle, cryopexy and external drainage of subretinal fluid at the SCOTS facility. He was referred to another facility for recurrent retinal detachment due to proliferative vitreoretinopathy (PVR) and underwent pars plana vitrectomy, pars plana lensectomy, membrane peel, endolaser, fluid-air exchange and silicone oil injection, at which time the retina was reattached and the vision improved to 20/300.[22]

Another case report involved a woman with retinitis pigmentosa who developed PVR/thick epiretinal membrane (ERM) following intravitreal injection of "autologous stem cells." Following vitrectomy and partial peeling of the ERM, histopathological analysis revealed the presence of CD34+ cells, likely from bone marrow-derived cells.[23]

Umbilical-tissue-derived cells, which contain a mix of mesenchymal stem cells, placenta-derived calls and dermal fibroblasts, are isolated from the neonatal umbilical cord. Janssen Biotech is conducting a trial using a microcatheter through the sclera and choroid to deliver umbilical-tissue-derived cells to the subretinal space for geographic atrophy.[24] Since these umbilical cells do not generate retinal tissue, the theoretical mode of effect would be indirect, through secretion of cytokines that might preserve the recipient's retinal cells. As yet, there has been no formally published report on this trial.

Autologous adipose-derived cells, collected from liposuction, have been proposed as intravitreal cell therapy for dry AMD. Bioheart Inc. sponsored a study using this approach, but the study has since been suspended. A similar trial in Russia is currently enrolling patients with open-angle glaucoma; it will involve sub-Tenon's administration of adipose-derived cells. To our knowledge, no reports have been published on the results of this or other adipose-cell-based trials.

While no FDA-approved stem cell treatments for retinal diseases are yet available, the evidence from early phase trials supports feasibility. There remain important caveats, however, including uncommon but serious adverse events such as endophthalmitis, PVR and retinal detachment.

To date, no Level One evidence exists to support that these therapies improve vision, but it is important to keep in mind that these early phase trials are not powered to detect efficacy. Larger, prospective and controlled trials are needed to determine whether statistically significant, meaningful visual improvements are possible with cell therapy strategies. The answers to these crucial questions should arrive soon enough. RS

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MIVS and Post-op Endophthalmitis

A look at evolving trends and techniques. **By David R.P. Almeida, MD, MBA, PhD; Philip I. Niles, MD, MBA; Peng Yan MD; Tina Felfeli; and Eric K. Chin, MD**

The era of micro-incisional vitrectomy surgery (MIVS) has caused us to re-think how we treat endophthalmitis. Where the Endophthalmitis Vitrectomy Study (EVS) published more than 20 years ago demonstrated that immediate vitrectomy for endophthalmitis does not significantly improve visual outcomes in patients with better-than-light-perception vision at presentation,[1] one can now argue that the EVS represented large-gauge vitrectomy and may not be applicable today when smaller-gauge MIVS is more widely performed.

Interestingly, the EVS findings showed that 26 percent of patients had no pain on presentation and 14 percent did not have a hypopyon.[1] Additionally, 94.2 percent of cultures confirmed gram-positive bacteria, mostly coagulase-negative *Staphylococcus epidermidis*.[1]

Thanks to MIVS, today we feel that early vitrectomy for endophthalmitis may be of significant benefit because it removes the infectious material and vitreous debris that are paramount to accelerating the clearance of the infection and optimizing visual outcomes, respectively.

Where EVS relied on older vitrectomy techniques with known increased rates and severity of complications, such as retinal detachment and vitreous hemorrhage, MIVS in contrast provides a quicker and safer option for eyes with severe inflammation. We recently reported 10-year data that showed small-gauge vitrectomy for endophthalmitis yields final visual outcomes comparable to 20-gauge instrumentation.[2] *In vitro* laboratory testing revealed no significant difference in rates of culture growth for different vitrectomy gauge sizes or vitreous cutting speeds.[3]

Watch the Video

View the five-trocar/cannula approach to early vitrectomy for postoperative infectious endophthalmitis. Video available at: http://bit.ly/2aWlzk7

Our Approach For Endophthalmitis

Our preferred technique for infectious endogenous endophthalmitis is vitreous biopsy ("tap") via a short 25-gauge needle on a 3- or 5-mL syringe. This is followed by injection with intravitreal antibiotics at the pars plana in the clinic. The most common antibiotics we use are intravitreal ceftazidime 2.25 mg/0.1 mL and vancomycin 1 mg/0.1 mL. In cases of known serious penicillin allergy, intravitreal amikacin 400 mcg/0.1 mL could be considered.

Additionally, we often use intravitreal dexamethasone 400 mcg/0.1 mL as an adjunct to address the severe secondary inflammation when our suspicion for fungal etiologies is low. If we cannot obtain a vitreous sample because the vitreous fluid is too viscous, we obtain an aqueous sample for cultures instead via a short 30-gauge needle on a 1-mL syringe at the limbus. (Note: the aqueous samples in the EVS were positive in only 42 percent of eyes.[1])

The clinical presentation can sometimes worsen within 24 hours of antibiotic injection. If the patient shows no clinical improvement, we typically perform pars plana vitrectomy within 48 to 72 hours of initial presentation, with the idea that the vitreous acts as a culture medium for microorganisms. This is speculated to be the most likely cause of the low incidence of endophthalmitis following routine pars plana vitrectomy surgery.

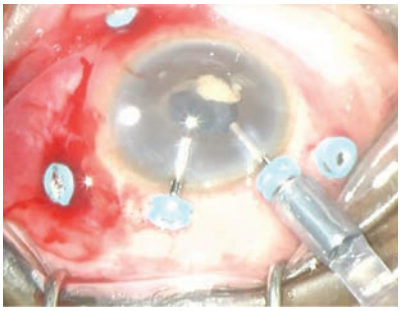

Figure 1. Early vitrectomy for postoperative infectious endophthalmitis involves a modification of the standard three-port posterior vitrectomy technique with two additional trocar/cannulas at the corneal limbus. The online video available at http://bit.ly/2aWlzk7 describes the technique in its entirety.

Five-trocar Setup

When the endophthalmitis does not resolve after our surgical technique described here, we employ a five-trocar setup using three standard pars plana trocar/cannulas and two limbal anterior trocar/cannulas (*Figure 1*). The latter two ports are typically necessary in cases of endophthalmitis complicated by significant anterior segment inflammatory reaction and/or media opacity.

We establish and verify the anterior infusion in the corneal limbus, using the second anterior cannula for anterior chamber washout and

Endophthalmitis: What We Know So Far

The most common form of infectious endophthalmitis tends to be exogenous (Figure 2), as opposed to endogenous, mostly following cataract surgery or intravitreal injection. It tends to present acutely within three to 21 days after the procedure. The timing of onset can help in identifying the infectious organism. Coagulase-negative Staphylococcus and Streptococcus, rather than Gram-negative organisms, typically cause acute-onset endophthalmitis within six weeks of an intraocular procedure.[7]

Chronic or delayed-onset endophthalmitis (beyond six weeks of intraocular surgery) is typically due to Propionibacterium acnes but may also involve Coagulase-negative Staphylococcus or fungi.[8] Bleb-associated endophthalmitis can occur months to years after filtering surgery and is most commonly caused by Streptococcus, Haemophilus or Gram-positive organisms. We previously reviewed 10 years of endophthalmitis cases (n = 758) and found Gram-positive organisms to be the causative pathogen in 80 percent of cases.[7]

Endophthalmitis incidence rates are difficult to determine because studies are usually under-powered, owing to its rare incidence after ocular surgery. The limited number of homogeneous study populations, different surgical techniques and variability in reporting methods make extrapolation of its prevalence difficult. Several reports have documented the evolving incidence of endophthalmitis, with rates varying from 0.03 percent to 0.345 percent.[1,3,9-16] Preoperative use of providone iodine anti-sepsis has the strongest evidence as a prophylaxis during intravitreal injection, with a Grade B recommendation.[17]

In post-cataract surgery endophthalmitis, the value of intraoperative intracameral antibiotics has been vigorously debated, with some authors suggesting they reduce the incidence of this devastating complication.[18,19]

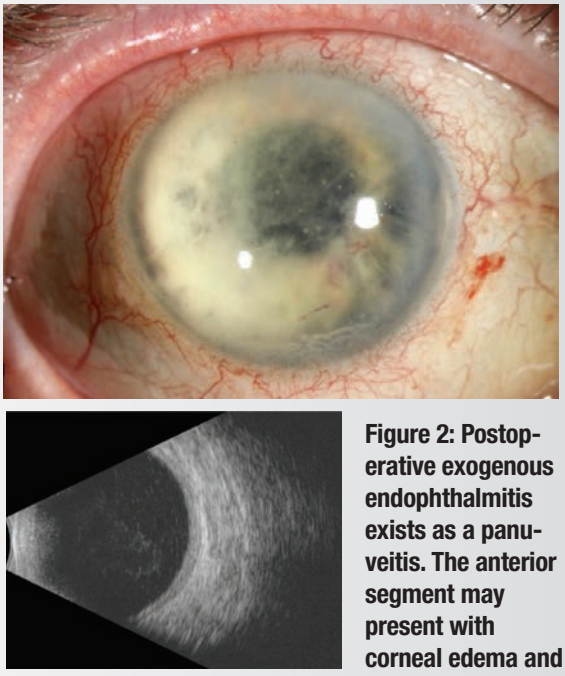

Figure 2: Postoperative exogenous endophthalmitis exists as a panuveitis. The anterior segment may present with corneal edema and marked anterior chamber cellular reaction in addition to a fibrin inflammatory membrane over the psedophakic posterior chamber intraocular lens (top). The posterior segment typically has vitritis (seen here on echography, bottom) with retinal hemorrhages.

membranectomy of fibrin and inflammatory membranes with the vitreous cutter and/or retinal forceps. When media clarity improves and we can better visualize the posterior segment, we can move the infusion line of a balanced saline solution to the pars plana and then perform a complete posterior vitrectomy. In cases where we still cannot visualize the pars plana infusion, we can perform posterior vitrectomy with the anterior infusion cannula.

Antibiotic Therapy

Another point of contrast to the EVS concerns systemic antibiotics. Although EVS showed no additional treatment benefit with systemic antibiotics, oral fourth-generation fluoroquinolones like moxifloxacin, which have excellent ocular and vitreous penetration, were not yet available.[2-4]

In cases of endophthalmitis, a 10- or 14-day course of oral moxifloxacin (400 mg daily) provides additional broad-spectrum coverage with good vitreous penetration. We tend to supplement this in a similar manner with topical fluoroquinolones, steroids and cycloplegia for added anti-microbial, anti-inflammatory and analgesia effects, respectively.

Although bacteria comprise the majority of causative pathogens in postoperative exogenous endophthalmitis, one needs to consider other organisms, such as fungi.[4] Additionally, we recently showed *Acanthamoeba* could cause an atypical postoperative panuveitis in a patient who underwent multiple penetrating keratoplasty surgeries. Our team is one of the first to histologically document *Acanthamoeba* involvement in all ocular layers with confirmed choroidal involvement.[6]

This example serves as a reminder for broad consideration when encountering suspected cases of infectious endophthalmitis. Active communication with patients and close follow-up of evolving clinical response are paramount to achieving the best outcomes. RS

Dr. Mandelcorn is an assistant professor of ophthalmology at the University of Toronto.

Dr. Almeida is a Canadian vitreoretinal surgeon with VitreoRetinal Surgery, PA, Minneapolis; Dr. Chin is with Retina Consultants of Southern

(Continued on page 48)

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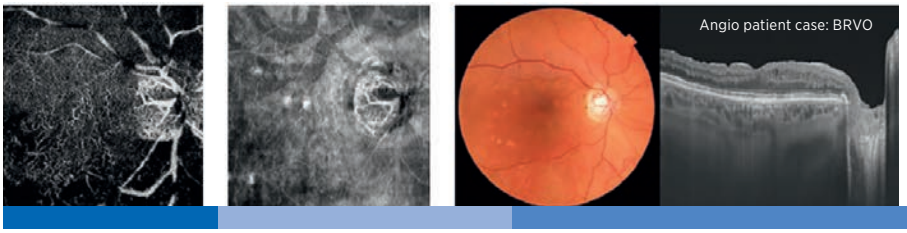

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By Kirk A. Mack, COMT, COE, CPC, CPMA »

Get Ready For ICD-10 Changes

The one-year reprieve ends October 1. Here's what you can expect and how to prepare.

About one year ago, we were concerned that chaos would occur and the claims processing system we rely on daily might collapse following the implementation of ICD-10. As we know, the system did not collapse and most claims were processed without incident.

The most common challenges occurred with coverage for diagnostic tests like optical coherence tomography scans. Some Medicare contractors omitted or overlooked adding some of the new ICD-10 diagnosis codes to Local Coverage Determinations (LCDs) that spell out coverage for particular services like surgical or diagnostic procedures. In several areas, new diagnosis codes were not on the October 1, 2015, LCDs, causing erroneous denials. The contractors were responsive to medical societies and individuals and updated the LCDs accordingly.

The Centers for Medicare & Medicaid Services (CMS) also stipulated in its July 2015 publication "CMS and AMA Announce Efforts to Help Providers Get Ready for ICD-10 Frequently Asked Questions" that, beginning October 1, 2015, they would not deny or audit claims as long as the diagnosis coding remained in the correct "family of codes" over the next 12 months. CMS stated:

> *While diagnosis coding to the correct level of specificity is the goal for all claims, for 12 months after ICD-10 implementation, Medicare review contractors will not deny physician or other practitioner claims billed under the Part B physician fee schedule through either automated medical review or complex medical record review based solely on the specificity of the ICD-10 diagnosis code as long as the physician/practitioner used a valid code from the right family.*[1]

Diabetes Changes

But the one year of leniency is ending. Combine that with multiple additions and some deletions to retinal conditions and there is significant preparation to do before October 1 this year. To begin, the diabetes mellitus (DM) sequences contain hundreds of changes in categories E08 through E13. The diabetic retinopathy codes now have laterality, making them seven digits. Laterality is represented in the seventh digit where "1" means right, "2" means left, "3" is bilateral and "9" unspecified. For example, we now have the following sequencing:

- E11.3511—Type 2 DM with [proliferative diabetic retinopathy] with macular edema, right eye.
- E11.3512—Type 2 DM with PDR with macular edema, left eye.
- E11.3513—Type 2 DM with PDR with macular edema, bilateral.
- E11.3519—Type 2 DM with PDR with macular edema, unspecified eye.

In addition to laterality throughout the diabetic sequences, multiple combination codes describing other diabetic complications exist in the update. Specifically, codes associated with retinal detachments include the following ("_" is the place for the laterality code):

- E11.352_—Type 2 DM with PDR with traction retinal detachment involving the macula.
- E11.353_—Type 2 DM with PDR with traction retinal detachment not involving the macula.
- E11.354_ Type 2 DM with PDR with combined traction retinal detachment and rhegmatogenous retinal detachment.

ICD-10-CM also added the following codes for stable PDR and PDR without macular edema ("_" is the place for the laterality code):

- E11.355_—Type 2 DM with stable PDR.
- E11.359_—Type 2 DM with PDR without macular edema.

AMD Changes

Several other areas in the "H" chapter contain additions. Last year, many physicians voiced their disappointment when age-related macular degeneration did not at least have laterality. H35.31 (nonexudative AMD) and H35.32 (exudative AMD) are now header categories requiring greater specificity, including laterality. In contrast to the change noted for diabetic retinopathy, the sixth slot for AMD represents laterality (right, left, bilateral) while the seventh slot represents staging of the disease. For example ("_" is the place for the staging code):

- H35.311_—Nonexudative AMD, right eye.
- H35.312_—Nonexudative AMD, left eye.
- H35.313_—Nonexudative AMD, bilateral.
- H35.319_—Nonexudative AMD, unspecified eye.

The code requires a seventh digit

designating staging as follows:

- 0—Stage unspecified.
- 1—Early dry stage.
- 2—Intermediate dry stage.
- 3—Advanced atrophic without subfoveal involvement advanced dry stage.
- 4—Advanced atrophic with subfoveal involvement.

Putting it all together, the code for a patient with bilateral intermediate dry AMD is H35.3132.

Similar changes to exudative AMD include laterality with the different stages of wet AMD also defined by the seventh character.

- H35.321_—Exudative AMD, right eye.
- H35.322_—Exudative AMD, left eye.
- H35.323_—Exudative AMD, bilateral.
- H35.329_—Exudative AMD, unspecified eye.

The required seventh character stages for wet AMD are as follows:

- 0—Stage unspecified.
- 1—With active choroidal neovascularization.
- 2—With inactive choroidal neovascularization with involuted or regressed neovascularization.
- 3—With inactive scar.

A patient with wet AMD with active CNV in both eyes is coded as H35.3231. Unfortunately, diagnosing AMD is no longer as simple as H35.31 for dry and H35.32 for wet. Staging and laterality are now required components.

Vein Occlusion Changes

Central and branch retinal vein occlusion (CRVO and BRVO) diagnoses change notably. We currently use H34.81_ for CRVO and H34.83_, with the sixth digit representing the eye, similar to AMD. The changes include adding the seventh slot to describe associated macular edema or neovascularization as:

- 0—With macular edema.
- 1—With retinal neovascularization.
- 2—Stable (pre-existing CRVO or BRVO).

Before October 1, we would be using two ICD-10 codes for BRVO with macular edema.

Preparation

In preparing for October 1, several areas deserve attention:

- Acquire a new ICD-10 CM manual. CMS has a free version.[2]
- Speak with electronic health record and practice management system vendors to insure updates are complete.
- Update cheat sheets.
- Review LCDs from Medicare and other payer policies for updates for diagnostic testing. Watch for effective dates on or after October 1, 2016.

These items represent some of the many changes effective October 1 relevant to retina subspecialists. Review the updated ICD-10-CM manual for additional changes. Leniency is about to end. Avoid using "unspecified" codes, unless you have no other choice.

Mr. Mack is a senior consultant with Corcoran Consulting Group. He can be reached at 1-800-399-6565 or at www.corcoranccg.com.

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North of the Border: MIVS

(Continued from page 45)

California in Redlands.

DISCLOSURES: *Dr. Almeida disclosed relationships with Allergan, Citrus Therapeutics and Genentech. Dr. Chin disclosed a relationship with Citrus Therapeutics.*

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Benchmarking Tool Can Track Coding

Retina PractiCare tool can show how your claims compare with peers'—and maybe help keep auditors away. ***By Richard Mark Kirkner***

The Office of Inspector General (OIG) last year cast a pall over ophthalmologists in general and retina specialists in particular. An OIG report focused on questionable Medicare billing practices among ophthalmologists for two diagnoses—age related macular degeneration and cataracts.[1]

Essentially, the OIG recommended the Center for Medicare & Medicaid Services step up it's monitoring of ophthalmologists, and then initiated audits against several retina practices.

Using that scenario as a backdrop, John Thompson, MD, of Retina Specialists, a three-office practice in Maryland, described at the 34th annual meeting of the American Society of Retina Specialists the society's benchmarking program, called Retina PractiCare, to help members monitor and track their coding habits.

Closing the Data Gap

"The use of big data against physicians is allowing Medicare and insurers to troll claims data to identify what they call 'high-cost physicians' and to punish them," Dr. Thompson said. "The combination of this physician profiling, payer reviews and uncertainty around appropriate billing practices has resulted in an inequitable environment for physicians, and physicians lack to the data to determine if they are outliers and likely to attract the attention of auditors."

Retina PractiCare aims to close that data gap. ASRS members who sign up can see how their claims patterns compare with not only peers in the same region and around the country, but also with partners in their own practices. Retina PractiCare does not identify participating physicians and practices except to fellow physicians in the same practice. "Large practices in a region don't have to fear they'll be identified," Dr. Thompson said.

Retina PractiCare securely downloads anonymized data from Medicare 1500 forms and aggregates the data with other retina specialists. All protected health information is removed before the data uploads to the Retina PractiCare servers.

The system is HIPAA compliant and protected health information does not leave the physician's server. "It will tell you if your practice is an outlier and you are at great risk of audit or terminations; or perhaps your practice is too conservative and you're not being reimbursed fairly for what you deserve," Dr. Thompson said.

Telling Trends in Coding

As of the ASRS meeting last month, 327 retina specialists from 62 practices have signed up for Retina PractiCare with "several million individual claims" in the database, Dr. Thompson said.

The data collected so far provides a picture of how retina specialists bill, and has shown some telling disparities, Dr. Thompson noted.

"The most common procedure performed by a retina specialist is an optical coherence tomography (92134) in over 40 percent of all office visits, followed by intravitreal injection (67028) in over 25 percent of office visits and level 2 return patient eye exam (92012) in 25 percent of claims," he said. "There are substantial variations in coding practices by individual retina specialists."

Some retina specialists use exclusively level 5 Evaluation & Management codes for all returning patients, while most use the eye codes because the reimbursement is better. Some practices uses the -25 modifier more than 80 percent of the time for intravitreal injections; others rarely use it.

Variations Within a Group

Dr. Thompson also shared tracking data of a group practice that showed wide variability among its own doctors' submitted claims. "This group can't seem to agree on using the -25 modifiers," he said. "We have different members of this group using the -25 modifier with intravitreal injection from 5 percent to 90 percent of the time," he said.

Likewise, surgery codes for retinal detachment vary. Dr. Thompson showed an example of a physician who bills complex retinal detachment for every RD case, while another does of mix of pneumatic retinectomies, vitrectomies and a few complex RDs. Another physician does extended ophthalmoscopy in 90 percent of exams while others rarely use it.

Dr. Thompson said Retina PractiCare has already had an impact in his practice. "It has changed the way I do some billing. I realize I was too aggressive in some areas and too conservative in other areas."

A little tweaking can help keep those auditors away.

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

Drugability of the Suprachoroidal Space

Phase II trial shows Clearside's CLS-TA safe and effective in noninfectious uveitis.

You could say getting drugs to the back of the eye has been retina specialists' Everest, but that wouldn't be fair to the Sherpas who guide climbers up world's highest summit. After all, thousands have stood on that summit, whereas the best solution science has had for getting drugs to the retina is intravitreal administration of anti-VEGF agents and corticosteroids. That typically involves serial injections because the concentration of the drug dissipates in the vitreous and washes out over time.

Clearside Biomedical (Alpharetta, Ga.) is taking a different route to the back of the eye—that is, via the suprachoroidal space. While not at the summit, it is somewhere on the mountain. Clearside uses a proprietary injector that penetrates the sclera, to uniquely access the suprachoroidal space, depositing a proprietary suspension formulation of triamcinolone acetonide. Called CLS-TA, the platform has been in multiple clinical trials, but the most noteworthy so far is the Phase II trial in noninfectious uveitis, which Steven Yeh, MD, reported on at the 34th annual meeting of the American Society of Retina Specialists in San Francisco.

In the trial, 22 eyes of 22 people with macular edema associated with noninfectious uveitis each received a single suprachoroidal injection of CLS-TA—a 4-mg dose in 17 people and an 0.8-mg dose in five. The primary efficacy endpoint was reduction in central subfield thickness, which averaged a 164-µm change from baseline (p=0.002) in the 4-mg group. The trial was only powered for the higher 4-mg dose and achieved a secondary efficacy endpoint—an average gain of 9.2 letters in best-corrected visual acuity from baseline. As for safety endpoints, no subjects showed steroid-induced increases in intraocular pressure or serious adverse events in this study.

"The outcomes from our Phase II trial provide preliminary evidence that CLS-TA has a positive effect in subjects with uveitis when it was administered suprachoroidally," says Glenn Noronha, PhD, chief scientific officer of Clearside. Here, Dr. Noronha provides insight into CLS-TA.

Quotable

> "The outcomes from our Phase II trial provide preliminary evidence that CLS-TA has a positive effect in uveitis when it was administered suprachoroidally."
>
> — Glenn Noronha, PhD

The mechanism of action in his own words:

Triamcinolone is a synthetic glucocorticoid with known anti-inflammatory and immunomodulatory properties, so the effect of this molecule in uveitis is reasonable. Specific to reduction of macular edema, there is speculation about suppression of vascular endothelial growth factor expression and restoration of the blood-retina barrier playing a role. None of the mechanistic aspects of how CLS-TA works in noninfectious uveitis will be unique in our product.

What is unique is not how CLS-TA works, but that in this approach to therapy the drug is administered through the suprachoroidal space, and that there is potential to provide safe and efficacious treatment as seen from the results of this trial. CLS-TA apparently achieves adequate ocular levels in the retina and choroid over the time period of the trial, and that could explain the efficacy reported in this Phase II study.

Why target macular edema in noninfectious uveitis?

Macular edema is the dominant cause of vision impairment and loss in uveitis. This trial targeted macular edema due to uveitis because of a unique opportunity to treat subjects with any etiology of uveitis, and with disease affecting any geographic location in the eye including anterior, intermediate, posterior and panuveitis.

The presumed advantages of suprachoroidal injection:

The advantages span from efficacy and duration, as well as the possibility for better safety. What happens after suprachoroidal administration of the drug is that it distributes dominantly into the retina and choroid, sparing the anterior chamber. Concentrations are high in the relevant parts of the eye, providing potential for good efficacy. Clinical trial data have been consistent with that expectation so far.

How the unique injector works:

The injector itself uses a needle about 1,000 µm in length. The sclera has a limited capacity to expand on

(Continued from page 52)

By Richard Mark Kirkner »

25 Years On, OCT Looks To Future

Co-inventor David Huang, PhD, shares the next big thing for today's big thing..

Today optical coherence tomography has become a staple in ophthalmology and all but standard of care in retina, but David Huang, MD, PhD, who has walked every step of the path of OCT since he and James Fujimoto, PhD, co-invented it 25 years ago, remembers when it wasn't so ubiquitous.

"If you were around in 1999, you remember retina specialists who said OCT didn't give them any information that they didn't already know," Dr. Huang said last month while addressing the Ophthalmology Innovation Summit at the American Society of Retina Specialists. "Today, these people are using OCT everyday."

Dr. Huang was a graduate assistant in Dr. Fujimoto's engineering lab at Massachusetts Institute of Technology in 1991 when they co-invented OCT. Drs. Huang and Fujimoto are co-editors of a special issue of the journal *Investigative Ophthalmology & Visual Science* commemorating the 25th anniversary of their invention.[1] More than 70 authors submitted papers on OCT for the issue.

What they started has now become a $1 billion worldwide industry that accounts for more than 2,500 jobs and more than 30 million OCT images that physicians capture each year.[1]

Today, Dr. Huang is a professor of ophthalmology and biomedical engineering at Casey Eye Institute at Oregon Health & Science University, and leads the Center for Ophthalmic Optics and Lasers Lab—the COOL Lab—at the institute. This year, as OCT commemorates its silver anniversary, Dr. Huang and his colleagues are more focused on the next 25 years of OCT. In an interview during OIS@ASRS, he provided insight into what's next for OCT.

David Huang, MD, PhD, (center in light blue shirt) with members of the Center for Ophthalmic Optics and Lasers Lab at Oregon Health & Science University Casey Eye Institute.

Even Faster Swept-Source OCT

While Dr. Huang doesn't believe OCT will be the beneficiary of infinite improvements, he does see the next phase in OCT development: much higher-speed, swept-source OCT. "That would improve the speed compared to current commercial systems, which run between 70 and 100 kHz; there's another factor of 10 by which that can improve," he says. "Eventually, the volume will be large enough that you can have OCT on a chip so that doctors can scan many beams and have it really compact and economic."

He also believes advances in OCT technology will make it even more accessible and affordable. "It will be more ubiquitous," Dr. Huang says. "It'll be much cheaper so that it can be brought down to the primary care level."

The Need for Speed

Dr. Huang considers the development of OCT angiography the most significant advance for the technology in the past five years. "It's going to really develop," he says. "We're going to learn how to interpret the images together with regular structural OCT: They're really synergistic; you get both from one scan anyway. It's not really a different data set; it's just different ways to process the same data."

Increasing the speed of OCT is vital for improving angioscans and

widefield scanning, Dr. Huang says, because the devices are so sensitive to motion they require volumetric scanning and skilled retinal photographers who can interact with patients in ways that minimize motion artifacts.

"These will eventually make photography a less-needed skill, make fluorescein angiography less needed and probably replace some function of the scanning laser ophthalmoscope systems as well in terms of widefield imaging," Dr. Huang says. "This will take several years to play out."

Further into the future, perhaps in 10 years or so, he sees greater use of intraoperative OCT by retina specialists.

Incubating in the COOL Lab

Meanwhile in Oregon, Dr. Huang and his colleagues at the COOL Lab are investigating greater applications of OCT beyond the retina—namely anterior segment OCT to measure corneal topography and epithelial mass to guide selection of intraocular lenses, perform phototherapeutic keratectomy and diagnose and manage keratoconus.

There's also what Dr. Huang calls the "big glaucoma project." He adds, "OCT angiography is a big part of that, but even within conventional-structure imaging there are a lot of advances that will continue to come out of this translational research, meshing the anatomy better and sorting out the hallmarks of glaucoma at a finer level."

The team is also working on novel contrast imaging. "We're looking at a nanoparticles contrast agent," he says. "That could be promising to be able to label cells and molecules with OCT imaging. That's always been a deficiency of OCT compared to scanning laser ophthalmoscopy and ophthalmoscopic fluorescein imaging."

Oximetry is another area where the COOL Lab investigators are taking OCT. That involves using spectroscopic contrast to measure oxygen levels in tissues. "That fits together with the angiography part as well," Dr. Huang says.

"I've worked on this for 25 years," Dr. Huang says. "I could probably work on this for another 25 years. I never run out of things to do." RS

REFERENCE

1. Fujimoto J, Huang D. Forward: 25 Years of optical coherence tomography. Invest Ophthalmol Vis Sci. 2016;57:OCTi-OCTii.

Drugability of the Suprachoroidal Space

(Continued from page 50)

account of its structure, and therefore injection of fluid through a needle into the sclera encounters resistance. However, as a needle extends towards the base of the sclera, resistance to expansion of the region between the base of the sclera and the underlying choroid—the suprachoroidal space—is far less. As a result, fluid containing the drug enters the space. Tactile and visual feedback assist in completing the injection.

Following suprachoroidal injection, fluid flows posteriorly and absorbs dominantly in the choroid and retina within minutes, based on observations from preclinical *ex vivo* models and animal studies. The expectation is that a rapid and selective distribution of drug would occur in human eyes in a similar manner to that seen in preclinical studies. The procedure has been relatively straightforward in more than 50 human subjects who have received these injections in Phase I/II studies.

The take home of the Phase II trial:

The trial observed good and consistent efficacy that includes visual acuity improvement and macular edema reduction; the objective is to see if a larger patient population will continue to show similar results when CLS-TA is dosed suprachoroidally to treat uveitis.

The big question the Phase II trial answers:

This study was a controlled, masked, randomized study that met the primary endpoint, which was a significant reduction in macular edema. Visual acuity also improved.

In uveitis, the trial showed that the suprachoroidal space is drugable and that there is potential to develop therapies by administering drugs through this space. The intention is to systemically define advantages of treatments via the suprachoroidal space through systematic developmental efforts. So the big question is, can you dose human eyes through the suprachoroidal space in this and other ocular disease states using CLS-TA and with other agents, and can you effectively treat eye diseases in this manner?

The next steps:

The first next step, a Phase III trial in uveitis, is currently enrolling. The second next step is to look at other disease conditions. To that end, a Phase II trial in retinal vein occlusion has already been completed. Those data will be shared soon for the first time. RS

Professional Opportunities

OPHTHALMOLOGY MEDICAL RETINA SPECIALIST

Bassett Healthcare Network
Bassett Medical Center

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

KEY BENEFITS OF THIS POSITION:

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

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

EEO EMPLOYER

FOR CONFIDENTIAL CONSIDERATION, PLEASE CONTACT:
Debra Ferrari, Manager, Medical Staff Recruitment,
Bassett Medical Center, One Atwell Road, Cooperstown, NY, 13326
phone: 607-547-6982; fax: 607-547-3651: email: debra.ferrari@bassett.org
or visit our web-site at www.bassettopportunities.org

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

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

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

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

Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

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

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

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

EYLEA® (aflibercept) Injection For Intravitreal Injection

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06/2016
US-LEA-1648(1)