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RETINA SPECIALIST

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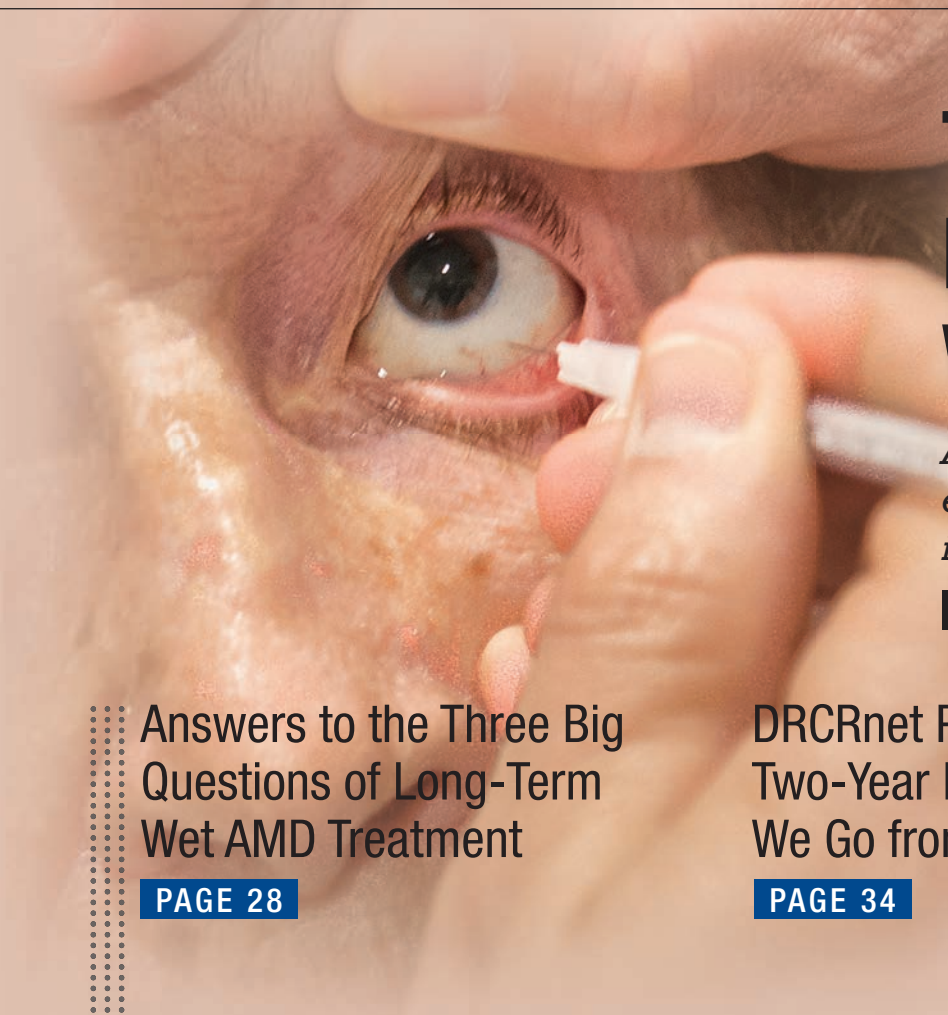

TREAT AND EXTEND FOR WET AMD

A conversation with two experts on the nuances of implementing TAE.

PAGE 22

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.

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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.

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By Charles C. Wykoff, MD, PhD

Forever, for Now

Doc, how many more shots?" Regardless of your detailed, diagram-assisted discussions, this question and its derivatives frequently resurface. "Doc, you said three shots, right?"

Wrong, at least for more than 90 percent of wet age-related macular degeneration patients. Many of us tell patients that wet AMD is like hypertension; we have good treatments, but similar to pills for blood pressure, they are not a cure and need to be given repeatedly, in many cases indefinitely.

Many of our long-term wet AMD follow-up analyses are sobering. Most recently, the patients who were examined five years after CATT enrollment were reported to have lost 11 mean letters compared to the two-year endpoint. The authors summarized bluntly, "visual gains … were not maintained."[1]

Possibly patients were under-treated after they completed the core two-year trial, because at five years 61 percent had intraretinal fluid and choroidal neovascular membrane area had grown by 59 percent while they received less than five mean intravireal injections annually. On page 28, Ivan Suñer, MD, MBA, and Marc Peden, MD, provide a perspective on optimizing long-term outcomes in this chronic disease: more frequent dosing translates into greater visual benefit.

While injection fatigue is often cited as a reason for reduced real-world treatment frequency, the majority of wet AMD patients appear to strongly prefer treatment regimens associated with the greatest amount of visual benefit, even if these involve a high treatment burden such as monthly injections.[2] Rather, it may be payers who most directly encourage injection fatigue given recent audits of monthly dosing of approved agents for wet AMD—even in the context of persistent exudative disease activity causing visual acuity loss. Under such scrutiny and financial duress, it becomes more palatable for doctors to accept intraretinal fluid in wet AMD eyes and extend treatment intervals beyond what is likely ideal for patients.

Pursuing individualized medicine, retina specialists continue to optimize approaches aimed at limiting treatment burden while preserving optimal outcomes. On page 22, Carl Regillo, MD, Jeff Heier, MD, and David Reed, MD, provide their tips for employing treat-and-extend dosing.

I tell my wet AMD patients, "It's not forever, forever. It's just forever for now. Until we have something better." Emerging treatments, including the novel VEGF-blocking agents brolucizumab (Alcon) and abicipar (Allergan), and dual-targeting therapies combining VEGF blockade with angiopoitin-2 and platelet-derived growth factor blockade hold great promise. Until new options are available, more frequent anti-VEGF dosing seems to be the best course to optimize long-term outcomes.

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1. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular Degeneration: the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology. April 20, 2016. [Epub ahead of print]
2. Mueller S, Agostini H, Ehlken C, Bauer-Steinhusen U, Hasanbasic Z, Wilke T. Patient preferences in the treatment of neovascular AMD: a discrete choice experiment. Ophthalmology. 2016;123:876-883.

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- Warren E. Hill, MD, FACS
Mesa, Arizona

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IMPORTANT SAFETY INFORMATION

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.

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.

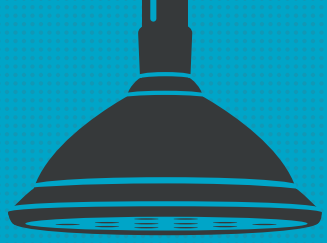
Warnings and Precautions

- 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 following page.



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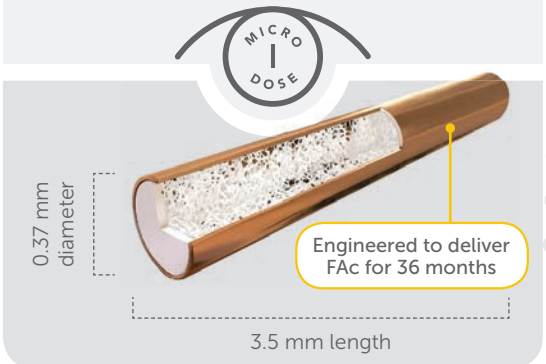
Continuous Microdosing™ for Continuous Therapy in Patients With Diabetic Macular Edema (DME)

ILUVIEN® has been implanted in over **5,000** eyes worldwide.[1]



ILUVIEN is a continuous microdosing delivery system™ specifically engineered 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 up to 36 months.[2-4]

Adverse reactions in the ILUVIEN phase III clinical trials were consistent with other corticosteroid treatments.[2]

Learn more at ILUVIEN.com.

1. Data on file. Alimera Sciences, Inc. **2.** Iluvien [package insert]. Alpharetta, GA: Alimera Sciences, Inc; 2014. **3.** 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. **4.** 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.

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

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ILUVIEN®
(fluocinolone acetonide intravitreal implant) 0.19mg

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

Table 1 (continued)

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

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

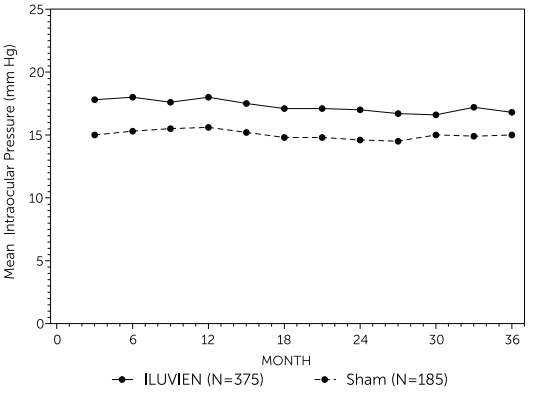
[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

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

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

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

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

USE IN SPECIFIC POPULATIONS

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

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A PUBLICATION BY REVIEW

RETINA SPECIALIST

Roger Barone/Wills Eye Hospital

JUNE 2016

FEATURES

DEPARTMENTS

IN BRIEF

- The **SEATTLE** Phase IIb/III clinical trial of **emixustat (Acucela)** did not meet its primary endpoint of showing a significant difference in the growth of lesions in geographic atrophy compared to placebo. Acucela said it will further analyze the SEATTLE data with its partner, **Otsuka Pharmaceutical**. Acucela also has an ongoing pilot study of emixustat for proliferative diabetic retinopathy and is considering an initiation study in Stargardt disease.

- **SanBio** has been granted a U.S. patent for its proprietary modified stem cells, SB623, for the treatment of retinal degeneration. SanBio developed SB623 to promote regenerative processes in the central nervous system and provide therapeutic options for debilitating neurological disorders, including retinal degeneration by enhancing photoreceptor function.

- **The Food and Drug Administration** has approved an update to prescribing information for **Eylea** (aflibercept, **Regeneron Pharmaceuticals**). The label language clarification recognizes that while most patients receiving Eylea will require dosing once every eight weeks after an initial monthly dosing period, some patients will still require monthly dosing.

- A retrospective analysis of the **Phase III RIDE** and **RISE** clinical trials, published in ***Ophthalmology***, showed that people with less advanced diabetic macular edema and who responded better to initial treatment with **ranibizumab** (Lucentis, **Genentech**) needed fewer injections over the long-term, suggesting that treating people with DME earlier may help reduce long-term treatment burden.

Conventional Thinking On Diabetic Retinopathy Turned Upside Down

The sequence of events in diabetic retinopathy is not what it has long been thought to be, researchers at the University of Iowa reported in the journal *PNAS*.[1]

For years, scientists believed patients developed retinopathy and, as a result of vascular damage, later developed neuropathy. Management had focused on early detection and treatment of retinopathy to prevent blindness and, subsequently, the nerve damage that neuropathy causes.

However, in this new study the Iowa researchers discovered that the sequence of events occurring in the retina from diabetes is just the opposite.

"What we're finding here, unfortunately, is that the nerve damage actually does come first, before the vessel damage," says Michael Abramoff, MD, PhD, professor of ophthalmology and visual sciences at the Stephen A. Wynn Institute for Vision Research and senior author on the study. "Even people with diabetes who never get retinopathy can still develop this damage, and after many years damage may be severe, similar to glaucoma."

Says Elliott Sohn, MD, first author on the study: "Essentially, the order of damage in the retina from diabetes is different from what we originally thought, and preventing the effects of retinopathy by itself would not protect the nerves in the retina."

In the study, Drs. Sohn and Abramoff and colleagues from Iowa and the University of Amsterdam studied 45 people with diabetes and little to no diabetic retinopathy over a four-year span. They found "significant, progressive loss of the nerve fiber and ganglion cell layer," proof of damage to the nerve before vascular changes typically found in the retina from diabetes.

At the same time, researchers found corresponding thinning of the nerve fiber layer in six donor eyes from patients with diabetes and little to no diabetic retinopathy. The layer was considerably thinner than the layer in six donor eyes from patients who did not have diabetes. Similar results were found in diabetic mouse models in this study.

Having a better understanding of the sequence of damage may lead to new treatments that focus on preventing the nerve damage and hopefully also prevent diabetic retinopathy, Dr. Abramoff says.

Quotable

"What we're finding here, unfortunately, is that the nerve damage actually does come first, before the vessel damage,"

- Michael Abramoff, MD, PhD

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Early Success With Stem Cells for AMD

Retina surgeons in Japan and the United Kingdom have reported the first successful stem cell transplants in individuals with age-related macular degeneration.

At the Association for Research in Vision and Ophthalmology 2016 meeting in Seattle, researchers from the Institute for Biomedical Research and Innovation Hospital in Kobe reported on a 70-year-old woman with exudative AMD who had stem cells implanted from her arm in 2014.[1]

Project leader Masayo Takahashi, MD, explained that the woman had already failed at existing treatments. The investigators collected a small piece of skin from the patient's arm and modified into induced pluripotent stem cells (iPSC). The iPSCs were then transformed it into retinal pigment epithelium sheets that were transplanted into the patient's eye. The transplanted cells survived without any adverse events for more than a year and resulted in slightly improved vision.

The woman maintained visual acuity at 18/200 without any additional anti-VEGF therapy, and her score on the Visual Function Questionnaire-25 improved from 40.7 to 58.3.

At the same time, retinal surgeons at Moorfields Eye Hospital in London reported on the first patient to undergo a stem cell treatment for wet AMD. The surgeons completed the first surgery last August with no complications.

This approach involved transplanting cells in the RPE with stem cells using a specially engineered patch inserted behind the retina in an operation that takes one to two hours. In all, the trial is recruiting 10 patients over 18 months and will follow the patients for a year.

"There is real potential that people with wet age-related macular degeneration will benefit in the future from transplantation of these cells," says retinal surgeon Professor Lyndon Da Cruz from Moorfields Eye Hospital, who is performing the operations and is co-leading the London Project.

REFERENCE

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Innovation Summit Comes to ASRS

The Ophthalmology Innovation Summit, which has brought together ophthalmic innovators and investors for the past several years at ophthalmology conferences, will add a third iteration at this year's American Society of Retina Specialists' (ASRS) meeting in August.

OIS@ASRS will take place on August 8, a day before the ASRS meeting starts. The program will include a showcase of emerging companies in retina, and sessions on financing and funding, retinal imaging, biologics, biosimilars and gene therapy, and combination therapies in retinal disease.

Among the scheduled speakers are Emmett T. Cunningham Jr., MD, PhD, MPH, summit chair; Tarek Hassan, MD, PhD, ASRS president; Dan Schwartz, MD; Cynthia Ann Toth, MD; Philip Rosenfeld, MD; Mark Humayun, MD, PhD, incoming ASRS president and recent recipient of the National Medal of Technology and Innovation from President Obama; Pravin Dugel, MD; Peter Kaiser, MD; Dan D'Amico, MD; and Gilbert H. Kliman, MD.

Also, Regeneron founder, President and CEO Leonard Schleifer, MD, PhD, and Tony Adamis, MD, vice president and global head of ophthalmology for Genentech, will participate in a "Masters of the Universe" session.

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By João Rafael de Oliveira Dias, MD, and Philip J. Rosenfeld, MD, PhD

Zika Virus and the Eye

A look at the evidence on the ocular effects of this mosquito-borne outbreak.
With Camila Ventura, MD

Zika virus (ZIKV) is an arbovirus that belongs to the *Flaviviridae* family and *Flavivirus* genus. While ZIKV is transmitted among humans by the Aedes mosquito species, such as *A. aegypti, A. albopictus,* and *A. africanus*[1] in the Americas, the main vector responsible for its transmission is *A. aegypti*. *A. aegypti* is the same vector that transmits dengue fever virus (DFV) and chikungunya virus (CHIKV).[2] Additionally, there have been reports of sexual, perinatal and blood transfusion ZIKV transmissions. However, the exact mechanism of transmission in these examples is still unknown.[3]

Moreover, the mechanism by which ZIKV causes fetal microcephaly is still unknown as well. Reports suggest that the virus is able to evade the normal immunoprotective barrier provided by the placenta,[4] and its neurotropic properties directly damage the brain during development. Alternatively, the placental response to the virus is the main cause of the brain damage since the virus can interrupt formation of the outer placenta, which might cause or contribute to microcephaly.[4]

The virus was first identified in 1947 in a rhesus monkey found in the Zika forest near Kampala, Uganda.[1] Five years later, it was isolated in Africans for the first time.[5] Then, the virus migrated to the Asian continent during the 1940s as a different strain from the one found in Africa.[6]

During the past two decades, the Asian strain has been causing outbreaks outside of Asia in other locations such as on Yap Island (Micronesia), in French Polynesia and on Easter Island in Chile.[7]

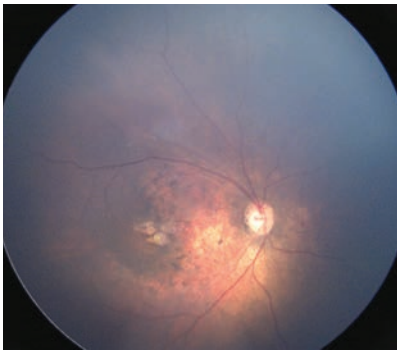

Figure 1. Wide-angle fundus image of the right eye of an infant with congenital Zika syndrome reveals an optic disc hypoplasia, gross macular pigment mottling and juxtafoveal chorioretinal atrophic lesions.

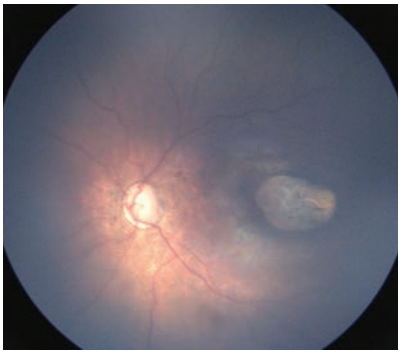

Figure 2. Wide-angle fundus image of the left eye of an infant with congenital Zika syndrome shows optic disc hypoplasia and a sharply demarcated area of chorioretinal atrophy in the macula.

However, the most recent and biggest ZIKV outbreak in history started in May 2015 in northeastern Brazil.[7] In 2015, an estimated 400,000 to 1.3 million people were infected by ZIKV.[7] The recent report of a possible association between ZIKV infection and an epidemic of microcephaly among neonates in Brazil has attracted significant global attention.[8]

This rapid spread of ZIKV beyond Africa and Asia to the Americas and Europe associated with the novel congenital Zika syndrome outbreak led the World Health Organization to declare this ZIKV epidemic a global public health emergency earlier this year.[9]

Systemic Manifestations

Only 20 percent of patients infected with ZIKV complain of mild symptoms such as headache, maculopapular rash, arthralgia and conjunctivitis, which usually last for one week.[4] Severe disease and fatalities caused by ZIKV were never previously described before the most recent studies from Brazil and French Polynesia, which described a neurotropism of the virus and the increased chance of Guillain-Barré Syndrome and other neurological manifestations.[2] Furthermore, microcephaly, hearing loss, limb abnormities and ocular findings were recently described as complications of ZIKV when the infection occurs during pregnancy.[2,10–12]

The current evidence of ZIKV infection relies on the molecular detection of viral RNA, which is positive only in a brief period of viremia. The currently available serological testing that identifies IgM and IgG antibodies specific for ZIKV is unreliable due to its cross-reactivity with other flaviviruses, and further studies are necessary to better elucidate these findings and their correlation to ZIKV.[13] Camila Ventura, MD,

and colleagues in Brazil recently published a study in which 40 infants with microcephaly were evaluated.[12] They tested using an IgM antibody-captured enzyme-linked immunosorbent assay (MAC-ELISA) of the cerebrospinal fluid in 24 of 40 infants (60 percent). All 24 infants had a positive MAC-ELISA for ZIKV in the cerebrospinal fluid; 14 were from 22 infants (63.3 percent) with ophthalmoscopic findings and 10 were from 18 infants (55.6 percent) without ophthalmoscopic findings.

Retinal Manifestations of ZIKV

A mild course of the disease can include anterior uveitis and a non-purulent conjunctivitis.[14] Dr. Ventura and colleagues published the first report of three children with presumed ZIKV congenital infection and ocular abnormalities.[15] They identified retinal alterations such as pigment mottling and chorioretinal atrophy in the macular region of the infants.

Further studies in two cities in northeast Brazil, Recife and Salvador, reported similar ocular abnormalities affecting the retina as well as optic disc abnormalities in these infants.[10–12] These findings included gross macular pigment mottling, macular chorioretinal atrophy, optic nerve hypoplasia, increased cup-to-disc ratio (*Figures 1 and 2*), iris coloboma and lens subluxation.

In a study conducted in Recife, nine of 20 eyes (45 percent) had optic nerve hypoplasia, pallor and increased cup-to-disk ratio.[11] The pathophysiology of these lesions in these infants is thought to be related directly to the virus or an associated toxin leading to an inflammatory reaction. In addition, this same mechanism could be responsible for the severe cerebral findings, such as abnormal development and cerebral calcification.

Dr. Ventura and colleagues[12] hypothesized that ZIKV may cause more severe ocular abnormalities when the infection occurs in the first or second trimester of pregnancy, as it does in other congenital infections such as toxoplasmosis, rubella and cytomegalovirus. Furthermore, other unknown factors, such as the amount of virus in the circulation and the immunologic response of mother and/or fetus, may play an important role in the formation of these abnormalities in newborns.[11]

Future Perspectives

Further efforts are needed to understand the pathogenesis of the ocular manifestations, to develop specific antiviral therapy and to facilitate vaccination against ZIKV and other arboviruses. First and foremost, mosquito eradication programs are critical to reduce the infection rates of ZIKV and other mosquito-borne illnesses such as DFV and CHIKV. These efforts are already underway globally and rely primarily on environmental modifications.

Furthermore, genetic manipulation of mosquito populations, such as the recently described gene-drive system that can introduce female sterility into a target vector population, may enhance these efforts.[16] RS

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TB or Not TB? That Is the Question

Did a complex interplay between TB and high myopia create a unique clinical entity?

By Jiun Do, MD, PhD, and Ehsan Mozayan, MD

A 39-year-old Vietnamese woman presented to the University of Southern California Roski Eye Institute complaining of metamorphopsia and photopsias in her right eye starting three weeks before her appointment. She also reported similar but less prominent symptoms in her left eye for the past two years.

History and Examination

The patient is a practicing pharmacist who emigrated from Vietnam to the United States in her late teens. Her ocular history is significant for -9.00 to -10.00 D of myopia in each eye and is status post-bilateral LASIK. Her medical history is significant for tuberculosis (TB) with a positive purified protein derivative (PPD) test and chest X-ray findings, and she is status post-systemic treatment for three to four months.

On exam, visual acuity was 20/30 in the right eye and 20/25 in the left. Intraocular pressures, pupils and anterior segment examination were unremarkable. Dilated fundus examination demonstrated bilateral trace vitreous cell, bilateral peripapillary atrophy and peripheral lattice degeneration OU. Gray lesions superonasal to the disc were in the right eye, and depigmented scars in the left eye.

Macular optical coherence tomography on this initial visit was normal. Fluorescein angiography (FA) demonstrated lesions with blockage in the right eye and lesions with early blockage and late staining in the left eye (*Figure 1*).

Given the clinical history and findings, we were concerned for multifocal choroiditis (MFC) secondary to TB. We started the patient on four-drug anti-TB therapy as well as oral corticosteroids with close follow-up.

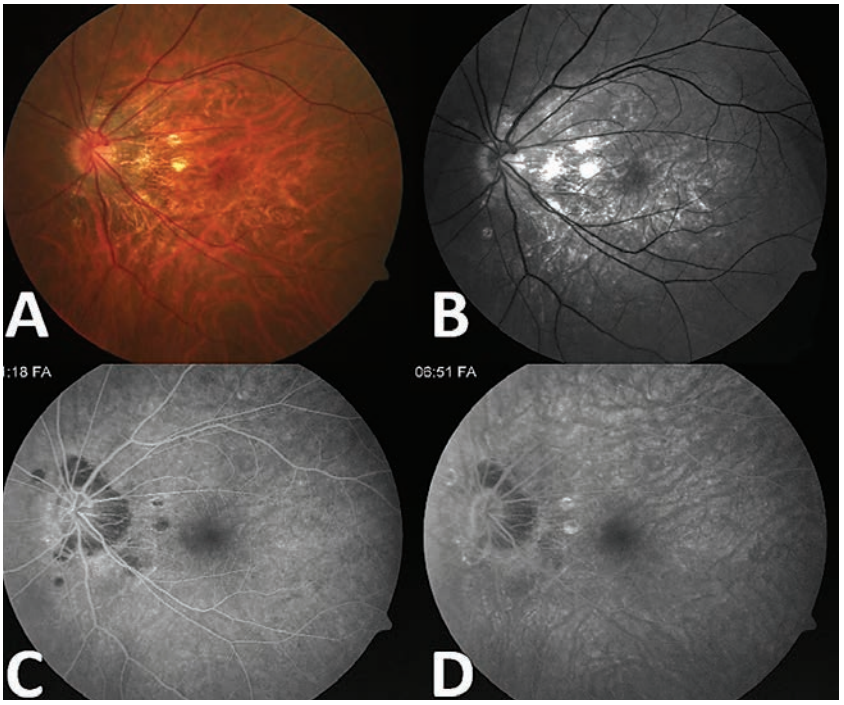

Figure 1. Fundus photo (A) and red-free image (B) of the left eye with peripapillary punched-out lesions. Fluorescein angiography shows early blockage and late hyperfluorescence/staining (C) consistent with multifocal choroiditis (D).

Three months after initial presentation, the patient reported acute worsening of vision in her right eye with 20/200 visual acuity. Repeat examination demonstrated new intraretinal hemorrhage in the macula of the right eye (*Figure 2A and B*), subretinal hyper-reflectivity with trace subretinal fluid on OCT (*Figure 3A*) and leakage in the fovea on repeat FA consistent with choroidal neovascularization (CNV) (*Figure 2C and D*).

Given the development of CNV, we initiated intravitreal bevacizumab (Avastin, Genentech) therapy.[1] After three monthly injections, the subretinal fluid resolved on OCT and visual acuity improved to 20/20 (*Figure 3 B, page 18*). The patient completed a nine-month course of TB treatment started during her initial visit but was then lost to follow-up.

Diagnostic Difficulties

CNV can be associated with decreased visual acuity or metamorphopsia secondary to subretinal or intraretinal accumulation of fluid, blood or lipid. The pathogenesis of CNV involves ingrowth of vessels from the choriocapillaris into the sub-pigment epithelial space with proliferation between the RPE and Bruch's membrane (type I) or between the RPE and photoreceptors (type II).

The differential diagnosis for CNV is broad and includes many etiologies, including age-related macular degeneration, pathologic myopia, angioid streaks and chorioretinal inflammatory conditions (i.e., presumed ocular histoplasmosis, MFC, multifocal evanescent white-dot syndrome and punctate inner choroidopathy). CNV may also be idiopathic.[2]

This case illustrates CNV either secondary to MFC from intraocular TB or pathologic myopia. Though the treatment of CNV is fairly standardized regardless of the etiology, identifying an underlying and treatable etiology, if present, is critical to prevent further episodes or complications.

Intraocular tuberculosis represents a diagnostic dilemma due to variations in presentation. Clinical symptoms, indirect systemic evidence including a positive PPD test or Quantiferon Gold and chest X-ray, the absence of other causes and a positive therapeutic trial suggest presumed ocular tuberculosis. Direct examination of ocular fluids by microscopic analyses, cultures and molecular techniques such as polymerase chain reaction can assist in a definitive diagnosis and provide rationale to initiate anti-tuberculosis treatment.[3]

High myopia is defined as more than -6.00 D or axial length greater than 26.5 mm, while pathologic myopia is defined as high myopia associated with typical fundus changes described later. Pathologic myopia is the most common cause of CNV in patients younger than 50 years and the second most common cause of CNV overall.

CNV may develop in 5 to 10 percent of eyes with an axial length greater than 26.5 mm. Findings associated with high myopia may include peripapillary crescents, disc tilting, posterior staphylomas and lacquer cracks.[2] FA can be helpful in the detection of lacquer cracks and identification of leakage associated with CNV. OCT in these cases of myopic CNV typically demonstrates hyper-reflective lesions with normal overlying retina, but intraretinal fluid, subretinal fluid and RPE detachment may also be observed.

Treatment Options

The standard treatment for TB includes a four-drug regimen (isoniazid, rifampin, pyrazinamide and ethambutol) for a two-month induction phase followed by four months of rifampin and isoniazid.[4] Prolonging treatment is considered under certain circumstances, and accommodations must also be made for multidrug-resistant TB. The addition of corticosteroids for intraocular TB may limit damage secondary to inflammation, but it should not be initiated in the absence of anti-tuberculosis treatment.[3] Treatment for CNV secondary to TB includes standard anti-VEGF therapy, modeled on the treatment of CNV secondary to AMD.

Treatment strategies for CNV secondary to myopic degeneration have included laser photocoagulation, photodynamic therapy and intravitreal anti-VEGF injections. The use of these therapies is extrapolated from studies evaluating the treatment of CNV in AMD. Photocoagulation is of limited utility when lesions involve the fovea and rates of CNV recurrence are high.[5] Photodynamic therapy enables treatment of sub-

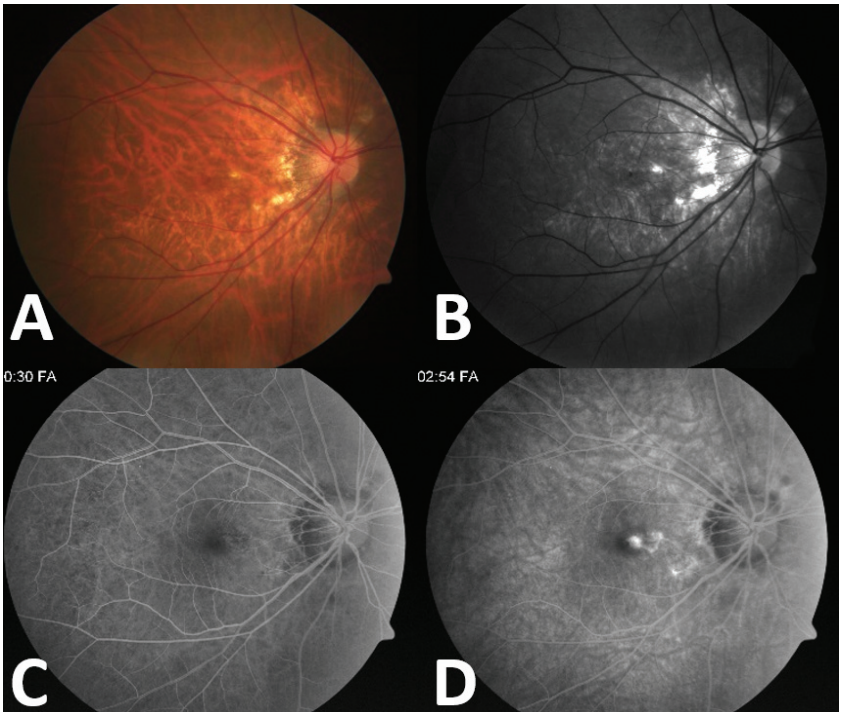

Figure 2. Fundus photo of the right eye on follow-up with parafoveal hemorrhage (A) and red-free image with small parafoveal blockage (B). Early (C) and late (D) fluorescein angiography show late fovea-involving leakage consistent with choroidal neovascularization.

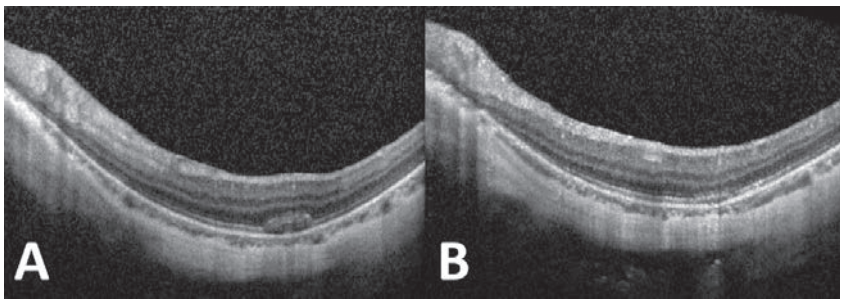

Figure 3. Optical coherence tomography of the left eye with representative subretinal hemorrhage before (A) and six weeks after (B) intravitreal anti-VEGF injection demonstrating resolution of subretinal hemorrhage and responsiveness to therapy.

foveal lesions, but it has been associated with decreased visual acuity, retinal atrophy and recurrence.[6] In contrast, prospective studies of anti-VEGF injections have demonstrated efficacy and safety.[1] Myopic CNV responds exquisitely to anti-VEGF therapy; a single intravitreal injection followed by PRN treatment is comparable to three monthly injections followed by as-needed injections.[7]

Patient Follow-up

Over the course of seven years, this patient continued to develop recurrent and new CNV in both eyes, which responded to anti-VEGF treatment. Given these recurrent episodes, she underwent an additional nine months of four-drug therapy for TB, thus completing three separate TB treatments in total. She continued to require intravitreal anti-VEGF on a PRN basis.

On her most recent follow-up visit, the patient had excellent visual acuity of 20/30 OU. Fundus examination demonstrated progressive chorioretinal atrophy compared to her initial evaluation seven years prior and a small intraretinal hemorrhage in the left eye (*Figure 4 A–D, page 20*).

FA demonstrated bilateral window defects, staining more prominent in the right eye than the left and blockage from the hemorrhage in the left

(Continued on page 20)

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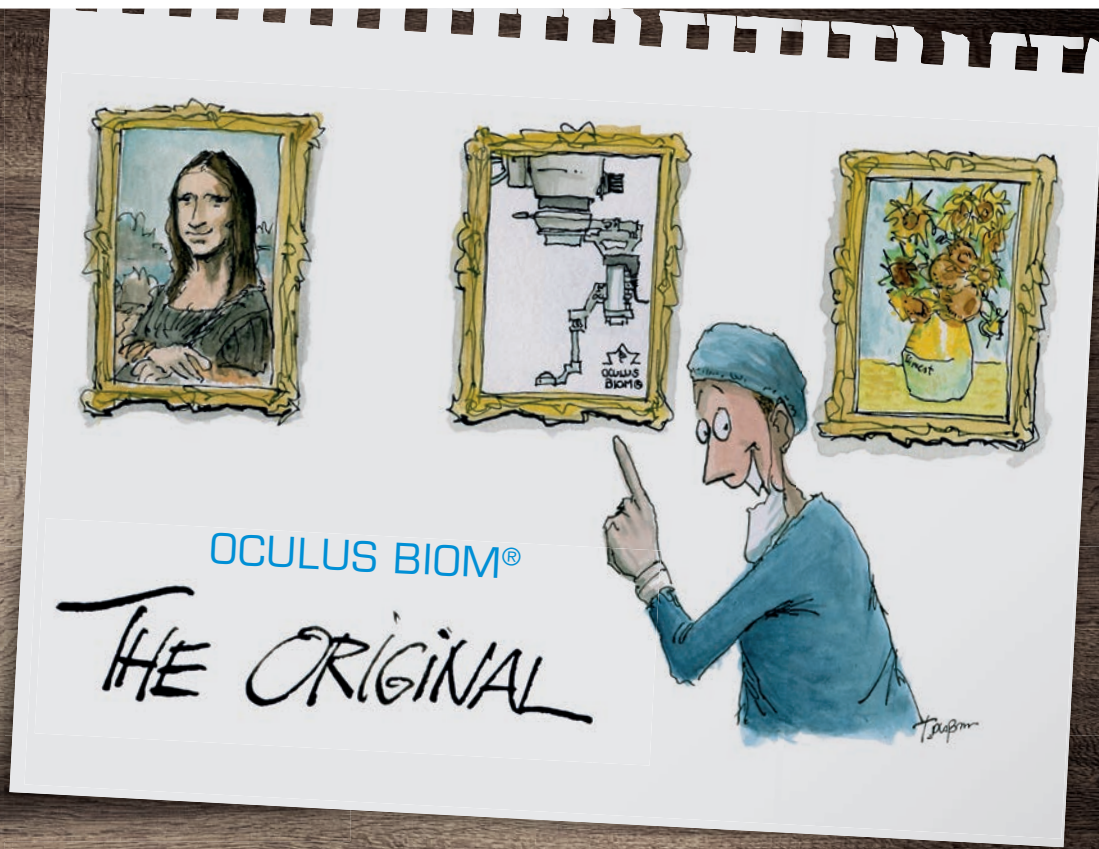

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By Paul Hahn, MD, PhD »

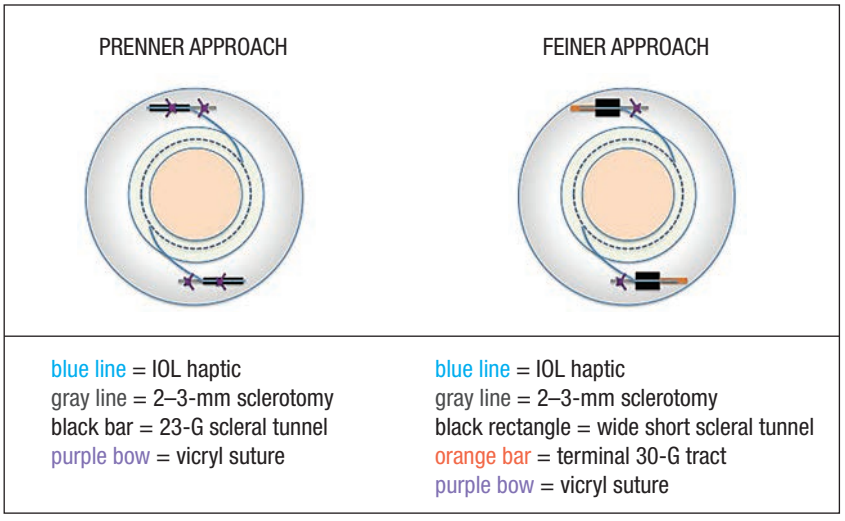
Tips for Sutureless Scleral Fixation

A close look at two approaches to make it work for you. ***With Jonathan Prenner, MD, and Leonard Feiner, MD, PhD***

Managing posterior segment complications of intraocular lens surgery has become an increasingly important responsibility of the retinal surgeon. Leonard Feiner, MD, PhD, and Jonathan Prenner, MD, introduced to the retinal community a technique of sutureless scleral IOL fixation.[1]

Briefly, this technique involves creating sclerotomies at 12 and 6 o'clock to externalize the haptics of a three-piece IOL, then passing the haptics through and securing them in an adjacent scleral tunnel (*Video*). I have always had difficulty with this technique as originally described. I found the approach to be technically challenging, and I often discovered IOL decentration in the immediate postoperative period.

In this article, I have the opportunity to share pearls from these two surgeons, who have each taken slightly different approaches to address these difficulties.



This schematic shows the two approaches for sutureless scleral fixation. In the Prenner approach, externalized haptics are passed through 23-G scleral tunnels with Scharioth forceps. In addition to closing the sclerotomies, a 7-0 vicryl suture is passed mid-tunnel around the haptics to stabilize the intraocular lens position in the postoperative period. In the Feiner approach, wide and short scleral tunnels (black rectangles) are dissected before the sclerotomy is created, allowing easy passing of the haptics with any forceps. The final step stabilizes the haptics in 30-G tracks (orange lines) created to follow the natural haptic orientation once the IOL has been centered.

Safely Externalize Haptics

One technical challenge is safe externalization of the haptics. Drs. Feiner and Prenner emphasize the need for a generous sclerotomy length. During externalization, Dr. Feiner uses internal limiting membrane-style forceps to "lasso" the haptic rather than directly grasping it to minimize damage.

Watch the Video

Jonathan Prenner, MD, describes important pearls to complete difficult steps in sutureless scleral fixation in a video available at: https://vimeo.com/168847970

If it is necessary to directly grab the haptic, Dr. Prenner will use a "handshake" technique to grasp the haptic tip directly with end-grasping forceps. Both feel that three-piece IOLs that have been in longer than five years have a significantly higher risk of haptic-optic separation. They prefer to exchange rather than rescue these lenses.

Pass Haptics Through Tunnels

Another technical challenge is safely passing the haptics through the tunnels. Dr. Prenner now uses Scharioth forceps (Dutch Ophthalmic USA) that have a longitudinal groove along their grasping end. When the forceps are closed, the tip is buried in the groove, and the closed forceps form a bullet-shaped end that minimizes the risk of engaging scleral fibers in the tunnel, for smooth passing.

Dr. Feiner has modified his approach and now instead creates 1.5-mm long scleral tunnels using an angled Beaver blade (Beaver-Visitec), as with tunnels for scleral buckling. The additional space in this wider and shorter tunnel makes passing of the haptics easy. These are placed prior to sclerotomy creation, in contrast to Dr. Prenner's 3-mm, 23-G tunnels, which are placed after.

Unexpected IOL Decentration

A final difficulty is unexpected IOL decentration or tilt in the immediate postoperative period.

To prevent this, Dr. Prenner now places a 7-0 vicryl suture in the middle of the 23-G scleral tunnel around the haptic to secure it while the sclera fibroses in.

In contrast, Dr. Feiner passes his externalized haptics (once passed through his wide but shorter scleral tunnels) through a 30-G needle tract that he creates as the last step. He directs the needle path based on haptic position once the IOL is centered to allow the haptics to sit naturally, as he believes committing to haptic positioning prior to placing the IOL is more likely to result in malpositioning.

Sutureless scleral IOL fixation is an important technique to maintain in a vitreoretinal surgeon's armamentarium. In addition to the approaches outlined here, a conjunctiva-sparing cannula-based approach and many others have been reported.[2] I encourage surgeons to try these various approaches. Read the literature, talk to surgeons who have performed them and make your own modifications to make this technique work for you. RS

Dr. Hahn is an associate at New Jersey Retina in Teaneck, where Drs. Prenner and Feiner are partners. Dr. Prenner is also an associate clinical professor at Rutgers New Jersey Medical School, Newark.

***Disclosures**: Dr. Hahn serves as a consultant for Second Sight Medical Products and Bausch + Lomb.*

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TB or not TB? That is the Question

(Continued from page 18)

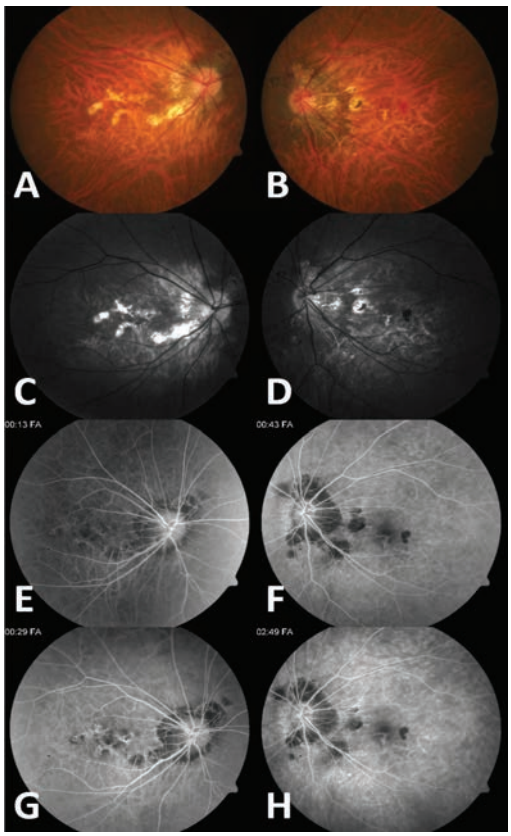

Figure 4. Fundus photos of the right (A) and left (B) eyes and red-free image of the right (C) and left (D) eyes from a more recent visit demonstrate bilateral, macula-involving chorioretinal atrophy compared to initial evaluation seven years prior (Figures 1 and 2) and a small amount of intraretinal hemorrhage in the left eye. Early fluorescein angiography (FA) of the right (E) and left (F) eyes and late FA of the right (G) and left (H) eyes demonstrate window defects and staining in the right eye and window defects and blockage in the left.

eye (*Figure 4E–H*).

This case represents a diagnostic dilemma in that both TB and high myopia can produce secondary CNV that is clinically indistinguishable. It is possible the complex interplay between these two created a unique clinical entity. Fortunately, with continued treatment of both her TB and her CNV, she has been able to maintain excellent visual acuity. RS

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TAE FOR WET AMD:

PRACTICAL TIPS FROM THE PROS

A conversation on the nuances of implementing treat and extend.

By David Reed, MD, with Jeffrey S. Heier, MD, and Carl D. Regillo, MD, FACS

While a brief description of the treat-and-extend (TAE) regimen for neovascular age-related macular degeneration gives the impression that it is a simplistic and formulaic protocol, practicing retina specialists recognize that its real-life implementation commonly requires nuanced clinical judgment. I recently had the opportunity to discuss with two top retina specialists, Jeffrey S. Heier, MD, and Carl D. Regillo, MD, FACS, how they handle the common scenarios not mapped out by a simplistic description of TAE.

Nuts and Bolts of TAE

Dr. Reed: Dr. Heier, can you please briefly outline the TAE regimen?

Dr. Heier: When using TAE, an injection is given at every visit, whether or not signs of active exudation are present. Treatment typically begins with monthly injections. If persistent signs of active disease are present, injections continue monthly until the macula is dry.

Once the macula is dry, the interval between injections is increased incrementally, often at one- to two-week intervals. If the exudation does recur, the interval between injections is reduced, thus finding the maximum interval that results in a dry macula.[1] Although the best results from the highest-quality data show that fixed monthly, or bimonthly in the case of aflibercept (Eylea, Regeneron), injections give the best visual results,[2-4] 66 percent of retina specialists in the United States use TAE[5] because they believe it rationally balances the goals of achieving good visual outcomes and reducing the number of injections given.

Dr. Reed: Many studies of TAE have used three monthly loading doses before attempting an extension. Dr. Regillo, do you use loading doses in your practice?

Dr. Regillo: I'll extend the first time I think the macula is dry or at its best. I take into account the vision, the exam, the optical coher-

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Dr. Reed is with Ophthalmic Consultants of Boston. He has received a research grant from Regeneron.

Dr. Regillo is with Mid-Atlantic Retina and the Retina Service of Wills Eye Hospital, Philadelphia. He has received research grants from Genentech, Regeneron, Allergan, Alcon, Ophthotech and Iconic, and has done consulting for Genentech, Regeneron, Allergan, Alcon and Iconic.

Dr. Heier is co-president of Ophthalmic Consultants of Boston. He has received research grants from Regeneron and Genentech, and had done consulting for Regeneron, Genentech, Heidelberg and Optovue.

ence tomography findings—all the data I gather at that encounter. Nobody has ever proven that loading doses are required. Many anti-VEGF studies used three loading doses because that is about the average number of treatments needed to get a macula dry.

Dr. Heier: If the macula dried up completely after the first injection, then I'll usually treat at that visit (resulting in two monthly visits), and then extend two weeks.

Dr. Reed: By what increment do you extend the interval when the macula is dry? If there is a recurrence while extending, by how much do you tighten the interval? What is the maximum interval you will extend to?

Dr. Regillo: I extend or reduce by two weeks. However, if a patient can't be extended beyond six weeks I'll use one-week increments to extend him as far as I can. So if the patient is recurring at six weeks but dry at four, I'll try five weeks. Although some patients can extend beyond 12 weeks, I don't routinely extend beyond 12 weeks. I think you're starting to roll the dice beyond that, regardless of the drug.

New Diagnosis of Wet AMD

Dr. Reed: Do you order a fluorescein angiogram for all new cases?

Dr. Regillo: I still routinely get an FA. There are some circumstances when I may not, but I like to be sure that I am dealing with wet AMD and not a condition that mimics wet AMD.

Dr. Heier: I do FA 100 percent of the time. I do it to understand exactly the characteristics of the pathology we're dealing with. I do it to make sure we're not missing other diseases, although that is less likely with spectral-domain OCT. It's less likely you'll miss cystoid macular edema or a small branch vein occlusion or macular telangiectasia, but it happens.

Figure 1. Carl Regillo, MD, FACS, delivers anti-VEGF treatment to a patient at Wills Eye Hospital.
Roger Barone/Wills Eye Hospital

I like to have the FA every time to document the pathology at the beginning. After that, I only repeat the FA if something has changed significantly or if the response is not what I would expect. For example, suppose I don't get a good response to bevacizumab (Avastin, Genentech), switch to aflibercept and still don't get a great response. I might repeat the FA and perform indocyanine green angiography as well.

Extension Despite Fluid or Blood?

Dr. Reed: Do you ever tolerate any fluid? For example, a recent consensus article suggested that two weeks of stable fluid on OCT would meet criteria for extending.[6] Do you agree with this?

Dr. Heier: Obviously my goal is to have the macula completely dry, but there are times I do tolerate fluid. If the macula does not dry out after the first few injections, I'm almost certainly still at a four-week interval. If I bring that person back at two weeks and the OCT looks the same, the fluid is likely relatively stable. I'll look at the OCT from when the patient was first diagnosed with wet AMD. If those initial scans were much worse and have now stabilized, I'll slowly extend, watching that fluid very carefully. That is a patient where instead of extending by two-week increments, I might

Take-home Point

Treat and extend for neovascular age-related macular degeneration requires a nuanced clinical approach. For example, while a completely dry macula is a goal, at times some fluid is tolerable—depending on the patient and clinical situation. Scenarios such as a recent cardiovascular event may dictate changing from treat and extend to as-needed treatment. In a nuanced approach, patient desires can play a significant role in treatment decisions.

extend by one week.

If the patient has significantly less fluid at two weeks than at four weeks, I would try increasing the dose of the injection at the next visit. We have substantial safety data on increased doses of both ranibizumab (Lucentis, Genentech)[7] and aflibercept,[8] and I will occasionally increase the dose by 50 to 100 percent from the same vial.

Dr. Reed: Are there characteristics of this persistent fluid that would make you more or less likely to tolerate it? Would you do an FA at this point to help you decide if the fluid was from active leakage?

Dr. Regillo: There are scenarios where the fluid is simply resistant to treatment. For example, in some patients, a small sliver of subretinal fluid overlying subretinal fibrosis will never completely go away (*Figure 2*). Small pockets of subretinal fluid at the edge of pigment epithelial detachments (PEDs) often don't indicate activity and are tolerated well (*Figure 3*). Small cysts can exist over fibrosis or over atrophy and do not necessarily indicate true choroidal neovascular (CNV) activity (*Figure 4*).

These examples of treatment-resistant fluid may be well-tolerated as long as there are no signs of true progression: vision isn't worsening and the CNV complex isn't growing. Repeating the FA can be valuable here. That's another benefit of having the baseline FA to compare with. If the disease is optimally controlled, you shouldn't see CNV growth. And if you're not seeing CNV growth, but you're seeing just a small amount of fluid that seems to be well tolerated, then it may be reasonable to not only tolerate it at a given interval but to also extend out as long as nothing changes.

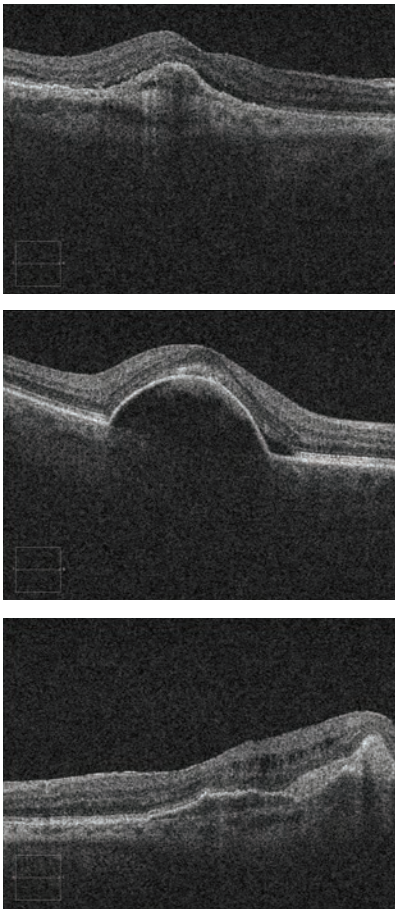

Figure 2 (top). A small sliver of subretinal fluid persists despite six monthly aflibercept injections. Visual acuity is 20/40.

Figure 3 (middle). A small pocket of subretinal fluid at the edge of a pigment epithelial detachment may not necessarily indicate true choroidal neovascular activity.

Figure 4. Small intraretinal cysts over an area of fibrosis persist despite eight monthly aflibercept injections. Visual acuity is 20/40.

Dr. Heier: Another modality that we are using and learning more about is OCT angiography. We are looking to see if there is a neovascular complex that is still active.

Dr. Reed: Suppose a patient could have injections every eight weeks with a small amount of persistent subfoveal subretinal fluid or injections every four weeks and be completely dry, with the same vision. Do you think the risk associated with doubling the injections is worth it?

Dr. Regillo: I wouldn't tolerate the fluid. I would try to extend to a five- or six-week interval and keep the macula completely dry. The recurrent fluid is not a good sign. We know that PRN or intermittent therapy doesn't work as well across the board because you're allowing for recurrences.[2] Over time, recurrent fluid is not well-tolerated and it could also be a sign of CNV growth, which you can't necessarily recover from.

We must think long term for this disease; it's for life for most of these patients. I tell every patient: We set out to get the best results with the fewest number of treatments. In general, allowing multiple or significant recurrences does not get the best results.

Dr. Reed: Suppose there is fluid and a small amount of intraretinal blood at the initial presentation. After the first injection, the fluid goes away but the small amount of intraretinal blood persists. Would you extend yet or wait until the blood is completely resolved?

Dr. Regillo: Usually I aim to get all signs of exudation to resolve before starting to extend. But I will sometimes tolerate a small amount of hemorrhage, especially if it's getting smaller and everything else has been dry for a while. As long as there is not new or increasing hemorrhage, I will tolerate some hemorrhage that remains after the initial hemorrhage and start to extend.

Dr. Heier: Absolutely. Often there are hemorrhages in lesions that persist for months, despite a dry OCT. Sometimes I'll look at the OCT angiogram, and if I don't see an active neovascular complex, I would extend.

Dr. Reed: If there is an RPE tear with hemorrhage, does that hemorrhage indicate activity in the same way as hemorrhage from CNV without a tear? Would you be more willing to tolerate the hemorrhage from a tear not involving the fovea than hemorrhage from CNV without a tear?

Dr. Heier: These are complicated cases and I watch them even more carefully. I've seen a number of these patients sent to me over the years where they had a tear and were ignored after the event. They were treated a little and extended more rapidly than I would have done, and then they had more bleeding. So I do watch these more carefully and make sure I am very aggressive with them as they heal. But at some point, very far down the road, if there is still some residual hemorrhage I may tolerate it.

No Recurrence at 12 Weeks: Now What?

Dr. Reed: How long do you keep patients at 12-week intervals before giving them a trial off injections? How frequently do you follow them once you do the trial off injections?

Dr. Regillo: Early on in the treat-and-extend paradigm, I would tell patients that if we can get to 12 weeks, the drug will have been long gone, and they will have shown they are stable without it. I used to routinely have patients come off treatment. Well over half the time they would eventually recur. Many other retina specialists noticed the same thing happening, so I very rarely stop treatment once a patient reaches a 12-week interval.

Another reason to keep them at 12 weeks is because I want to keep a close watch on both eyes. These people are at very high risk of having wet AMD in their fellow eye. And so I like having them come in at this interval, anyways. Sometimes I'll extend them to 14 weeks or I'll tell them 12-14 weeks is acceptable. I won't be as strict, for example, if it's a snow day or if the patient has scheduling issues.

Perhaps in the future there will be drugs that last longer. Two drugs currently in Phase III trials, Allergan's Abicipar and Novartis/Alcon's Brolucizumab (RTH258), may achieve greater durability than the drugs we use now.

Dr. Heier: I agree with Dr. Regillo. In the past I was more likely to stop treatment than I am now. The data convincingly shows that the less regular therapy we do, the worse patients do in general. If it's a monocular patient whose fellow eye had a neovascular event, I will never stop injecting the good eye. Some of those patients I may even keep at eight-week intervals, depending on what type of event they had.

Bilateral Wet AMD, Each Eye with Unique Needs

Dr. Reed: Suppose one eye requires injections every four weeks and the other requires injections every six weeks. Assuming you do bilateral injections, how do you handle this situation?

Dr. Regillo: I leave it up to the patient. I try to find some common ground and make it easy for the patient. If the patient doesn't mind coming more frequently, I will treat each eye on separate visits, but often the eye that requires more frequent injections drives the interval. If one or both of the eyes are extending, I will try to get them in sync if I can. There may be a time when I'll accelerate the extension in one eye and slow down the extension in the other to get them in sync.

When to Retry an Extension?

Dr. Reed: Suppose a patient had a history of recurrence at 10 weeks and has been stable receiving injections every eight weeks. How long would you keep him at eight weeks before you try to extend again?

Dr. Heier: I don't know what the right answer is, and it probably depends on the patient. It would be a minimum of six months and it might be even longer. It depends on what happened during the recurrence.

If it was a very subtle recurrence, perhaps I would try to extend again after four to six more injections. If the recurrence was fairly significant, where they had a loss of vision, or bleeding, then it might be even longer.

Dr. Regillo: It's variable and a hard question to answer precisely. The fellow eye plays a role in the decision. As Dr. Heier noted, what kind of recurrence they had also plays a role. It also depends on how good their vision is. If they have poor vision and they're not noticing these recurrences, then I may be more inclined to rechallenge them. But if they have good vision and they are exquisitely sensitive to any changes, I'd be less inclined.

I was involved in that consensus article you referred to and this was the one question that had the biggest debate. Our consensus was that you could consider rechal-

lenging the patient after two or three consecutive visits with maximal response.

Situations for Less Frequent Treatment

Dr. Reed: Are there scenarios where you would attempt to minimize injections even further, perhaps even use a PRN regimen?

Dr. Regillo: There are a couple scenarios where I might deviate from treat and extend and treat PRN. One is a recent stroke or myocardial infarction, where I'm worried about exposure of the drug systemically, even though I think the risk is very low. I would have a dialogue with the patient and say, "There is a small chance this could exacerbate your vascular disease and I want to try something to minimize the exposure even more than what we are already doing. Because with treat and extend we are already trying to minimize the exposure of the drug." So I might skip a dose and see what happens.

I might also use this approach in a patient with a history of endophthalmitis if the patient had a big scare. Especially in the process of trying to get the endophthalmitis to resolve, we're often taking a break from injections at that time. However, in the fellow eyes of patients who have had severe endophthalmitis, I still use TAE; I am not willing to use a strategy that will result in worse vision in their good eye.

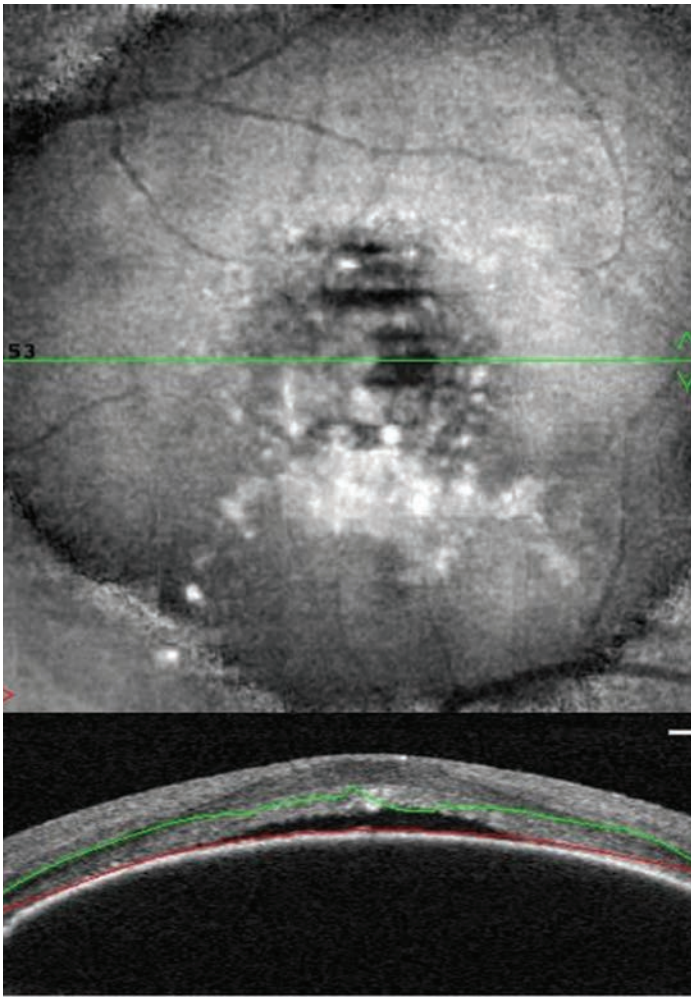

Figure 5. *En face* optical coherence tomography shows a large pigment epithelial detachment (top), while a cross-sectional OCT image shows the large pigment epithelial detachment with subretinal fluid at its crest.

Dr. Heier: The one that is the most important is the recent stroke or myocardial infarction. Both Dr. Regillo and I have given safety talks on these drugs and I think these drugs are remarkably safe. If there is an increased risk in patients with a recent cardiovascular event, that risk is very low.

Still, the concept of a cerebrovascular accident or cardiovascular event that may be related to our treatment, however unlikely, is concerning. I'll always have the discussion with these patients, telling them, "There's little to no evidence that these injections increase your risk if you haven't had a recent stroke or myocardial infarction, but there may be a slightly increased risk if you have. It's hard to know for sure because patients receiving these drugs are already at increased risk."

In this scenario, if the patient has good vision in both eyes and has been very well-controlled, I might try PRN treatment. If the patient has good vision in only one eye and the other eye has poor vision from AMD, or any other cause, I'm unlikely to stop treatment. In that case, I will have an in-depth discussion with the patient and his family. And I will bring into the conversation their neurologist or their cardiologist or their primary-care doctor because these patients are at high risk and I want them to understand that they are already at high risk because they've had a recent stroke. Many patients are already being anticoagulated, so their risk of another event may be relatively low, yet their risk of vision loss and resulting loss of independence is high.

If they've had a very mild endophthalmitis, I probably won't change very much. We'll discuss it and say, "This was a very rare

occurrence and the likelihood of it happening again is low. The likelihood of losing vision from under-treatment is not insignificant." And so we will likely continue. But if the patient had severe endophthalmitis with significant vitreous debris remaining, and the view of the posterior pole is poor, then often I will delay therapy.

When RPE Tear Is a Concern

Dr. Reed: What about the concern for causing an RPE tear in patients with a high PED (*Figure 5*)? And the concern for injections causing geographic atrophy? Does either of these concerns tempt you to treat less than traditional TAE?

Dr. Regillo: I definitely tell patients with a high PED that tears can occur, and we don't know whether it's precipitated by the drug or not. It can happen at any time. And we've all seen them happen without injections. So I'm not even sure of the causal relationship. I'm worried, but I don't deviate in this scenario.

We don't have evidence that these drugs are accelerating geographic atrophy. We probably never will. I don't reduce treatments because of this concern. However, if a patient whose wet component is under control is losing vision because his atrophy is becoming subfoveal or expanding, I won't reduce the interval. That's an important point to keep in mind when vision changes are affecting your decision to treat and how often.

Dr. Heier: I'm actually afraid to stop treating wet AMD patients with a large PED.

In patients with geographic atrophy, I will try to determine why the patient is losing vision. A lot of times patients who are doing very well with injections will complain of vision loss from the atrophy. That's a case where I'm concerned that the treatment could be accelerating its progression. If the fellow eye looks similar, I think that is their natural history. But still this is the patient for whom TAE is very valuable. Even in these situations I rarely go beyond three months.

Dr. Reed: If a patient has good vision in one eye but 20/400 in the other eye, and you're only injecting the bad eye, would you ever be less aggressive? For example, if the patient requires monthly injections to maintain a dry macula, would you continue on this regimen to maintain the 20/400 vision in the eye they're not using everyday?

Dr. Heier: This is a good question: When do you stop? If they are 20/400 and are stable, I'll tell patients there are two reasons to continue treatment. One is to make them better and the other is to prevent them from getting worse. If they have a reasonably small to moderately sized scar and whenever I stop they leak and their vision gets worse, then I'm going to keep treating them. Although we're not helping them to improve, we are preventing them from getting worse, and I'll continue to treat.

On the other hand, if we hold on treatment and their vision doesn't change, I might stop treatment. If we hold treatment and they get leakage and decreased vision and aren't bothered by it, I may consider stopping.

Dr. Reed: Suppose you hold injections in such a patient—one with poor vision who gets a recurrence of fluid, but no change in vision. Are you concerned that a decade with fluid might deteriorate his or her vision further than if you had continued injections?

Dr. Heier: I am, which is why I try to gauge whether I'm still making a difference with injections. If I can show I am making a difference, it makes a stronger case for continuing treatment. But some patients do tire out. Although I would like to be able to maintain that 20/400 vision, the patient's desires also play a role.

Also, we've all seen 20/400 eyes with relatively manageable scars and 20/400 eyes with large scars that are far less functional. The relatively wide range in what 20/400 means in terms of daily function also influences patients' desires to continue or stop treatment.

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ANSWERS TO THE THREE BIG QUESTIONS OF LONG-TERM TREATMENT OF WET AMD

Anti-VEGF agents have forced us to choose an agent and regimen, and learn when enough is enough.

Marc C. Peden, MD, and Ivan J. Suñer, MD, MBA

The advent of anti-vascular endothelial growth factor agents has revolutionized the treatment of wet age-related macular degeneration. These pharmacotherapeutic agents have resulted in not only preservation, but also improvement, of visual acuity and quality of life in the majority of our patients. However, they have also forced us, as retina specialists, to face three questions when it comes to treatment of wet AMD:

- Which agent do we use?
- How often do we give it?
- If and when should we stop treatment?

Multiple randomized, controlled clinical trials have demonstrated the short-term efficacy and safety of these agents. However, there has been a dearth of long-term data to guide us in our chronic management or to provide us long-term treatment expectations for our patients. Here, we try to answer those questions.

The Early Trials

Nearly 10 years ago, the two landmark ANCHOR and MARINA trials demonstrated the efficacy and safety of monthly ranibizumab (Lucentis, Genentech) over the course of two years. Patients gained 10.7 and 6.6 letters, respectively, at two years.[1-3]

Five years later, the parallel studies, VIEW1 and VIEW2, similarly showed improvement in vision with aflibercept administered every eight weeks after three initial monthly loading doses at the studies' one- and two-year endpoints.[4] Subsequent randomized multicenter trials have allowed us to evaluate the efficacy of these drugs compared to off-label bevacizumab (Avastin, Genentech), as well as to investigate other less-frequent dosing intervals, including quarterly and PRN regimens.

While each of these treatment strategies has shown benefit over observation, the visual acuity outcomes are inferior compared to monthly

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treatment. The PIER study examined quarterly dosing after three monthly loading doses, and, while superior to observation, PIER patients lost 2.3 letters from baseline at one year.[5] EXCITE compared quarterly dosing to monthly therapy and, once again, while the quarterly arms did not reach pre-specified non-inferiority compared to the monthly arm at one year, the results were clearly better with more frequent dosing.[6]

One of the earliest exceptions was PrONTO, a Phase I/II trial that involved 40 patients over two years on a monthly PRN basis using visual acuity, clinical examination and optical coherence tomography parameters as guidelines for re-treatment.[7] The visual acuity results approached those of ANCHOR and MARINA with nearly half the number of injections, but the study lacked a monthly-treatment control arm.

CATT and HARBOR had monthly and PRN treatment arms. While these studies demonstrated statistically similar results with monthly dosing in the short term, absolute data outcomes were almost unanimously superior with monthly dosing. What's more, long-term outcomes may reveal inferiority of alternative treatment strategies as the two-year results of the bevacizumab PRN group in the CATT trial showed.[8]

While the aforementioned studies have been crucial in guiding our management and treatment of exudative AMD, the treatment protocols can be onerous to adhere to in clinical practice. Many retinal physicians gravitate toward less-frequent examination and dosing regimens. Frank Holz, MD, and colleagues demonstrated that this has resulted in poorer visual outcomes in "real-world" clinical scenarios compared to published study results (*Figure 1*).[9]

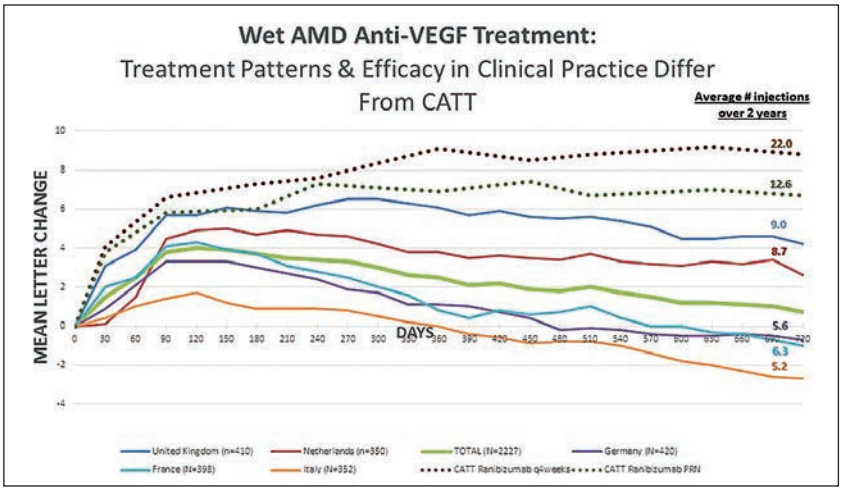

Figure 1. Under-treatment of wet AMD in clinical practice leads to visual outcomes worse than those seen in controlled clinical trials. In the studies cited here, decrease in mean visual acuity from baseline correlated to fewer injections.

Treat-and-extend regimens, as Michael Englebert, MD, PhD, and colleagues initially described them, however, offer a hybrid option that allows continuous dosing with less rigorous monitoring than PrONTO protocols, while resulting in fewer injections and visual outcomes similar to monthly dosing, at least in the short term.[10]

A recent retrospective study examining three-year outcomes reported visual gains comparable to other studies where patients received monthly therapy with an average of 6.4 yearly injections over three years.[10] While all of these studies offer guidance with regards to efficacy of various drugs and treatment intervals, they are limited to short follow-up (one to three years); thus they fail to address outcomes over prolonged treatment. Unfortunately, due to a lack of long-term outcomes data, physicians have been relegated to extrapolating this short-term data into the chronic management of wet AMD.

Long-Term Data, Such as It Is

CATT showed that visual gains of PRN dosing with bevacizumab were inferior to those with monthly ranibizumab after the first year. These discrepancies over time raised the question of whether additional temporal divergences might occur over the long term. Given the expense of large, randomized trials, treatment data has essentially been limited to two-year outcomes with a few exceptions mentioned herein. Only recently, with data from HORIZON, SEVEN-UP, FIDO, CATT

Take-home Point

Despite limited long-term evidence on efficacy of vascular endothelial growth factor (VEGF) suppression in the treatment of neovascular age-related macular degeneration and its role as a causative agent in geographic atrophy (GA), the evidence is accumulating that sustained anti-VEGF therapy improves visual outcomes and, perhaps, actually delays progression of GA.

and the observational study by Mark Gillies, MD, and colleagues, have we seen that a divergence in visual acuity outcomes between the various treatment regimens does indeed play out with time (*Figure 2, Table*).[11-15]

The HORIZON extension trial followed patients exiting from the ANCHOR and MARINA trials after two years of monthly therapy.[11] These patients then had treatment and monitoring on average every two months PRN. Within one year, the impressive 9-letter gain initially reported with monthly therapy dropped to 4.1 letters. Visual loss continued over the ensuing two years, with patients demonstrating a mean 0.1-letter loss from baseline.

An additional cohort from HORIZON was further evaluated in the SEVEN-UP study that added three years of follow-up of patients exiting HORIZON after four years of therapy.[12] They experienced further vision loss, ending up 8.6 letters below baseline (*Figure 2*). However, eyes only received an average of 6.8 injections over the 3.4 years after exit from HORIZON. Most notably, approximately 41 percent of eyes received no treatment at all.

A separate univariate analysis found that patients receiving 11 or more injections after exit from HORIZON actually gained 3.9 letters, ending up 5.6 letters better than baseline after seven years (*Figure 3*). It is important to note that PRN protocols seen in HORIZON/SEVEN-UP differed from standard PrONTO-based monitoring and retreatment criteria, which specify monthly monitoring. More stringent PRN protocols with prescribed OCT-guided retreatment may result in outcomes superior to these reported PRN results. However, once again, the long-term data is lacking.

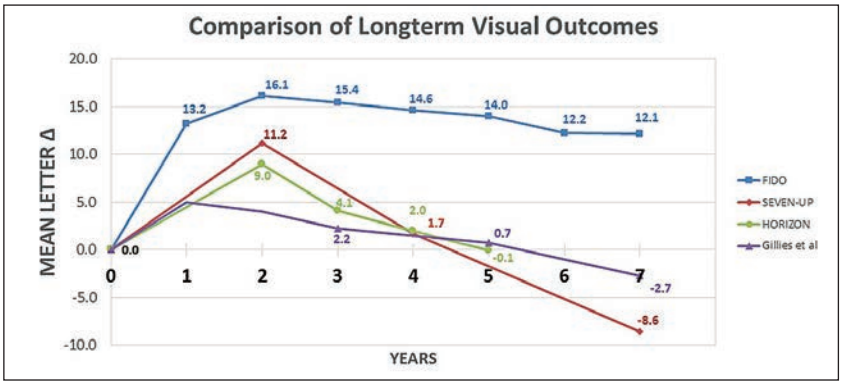

Figure 2. Long-term mean letter change over time in patients receiving anti-VEGF therapy for wet age-related macular degeneration.

Last year, an observational study reporting seven-year outcomes of treatment-naïve patients receiving anti-VEGF therapy at the discretion of 23 different specialists demonstrated slightly better results with a greater average number of injections.[14] Of the 131 eyes with the longest follow-up, a 2.7-letter loss from baseline was noted at seven years (*Figure 2*), with 40 percent of patients maintaining 20/40 vision compared to 32 percent at baseline.

Eyes received six injections on average in the first year, five injections between years two and five, and 5.5 injections in years six and seven. While this study did not report a percentage breakdown of the various treatment regimens, the authors did state that the majority of investigators favored a treat-and-extend approach—consistent with a higher average number of injections than the SEVEN-UP study. More injections, however, were also associated with improved visual outcomes when compared to SEVEN-UP.

The CATT trial most recently released its five-year data. The results were equally disappointing as the results seen in Dr. Gillies' observational studies, as patients lost a mean 3 letters compared to baseline and 11 letters from the two-year CATT outcomes.[15] After completing two years of the CATT protocol, patients were no longer evaluated and treated according to protocol, and physicians treated them according to their normal practice patterns with regard to frequency and agent.

Over the ensuing three years, there was a bias toward bevacizumab along with decreased frequency of treatment. Of the patients originally in the ranibizumab arms, 53 percent were treated with bevacizumab or bevacizumab in combination with ranibizumab and/or aflibercept (Eylea, Regeneron Pharmaceuticals). In the original bevacizumab arms, 62 percent were continued on bevacizumab alone or in conjunction with ranibizumab and/or aflibercept.

Furthermore, patients originally in the ranibizumab monthly and PRN arms received 10.7 and 5.7 injections in the second year of CATT, respectively, while those in the bevacizumab monthly and PRN arms received 11.5 and 6.8 injections in the second year, respectively.[8] Over the next three years, the combined cohort received an average of 4.8, 4.5 and 4.0 injections in the third, fourth and fifth years, respectively.

At five years, this difference

amounted to as much as a 65-percent reduction in treatment frequency for those eyes in the bevacizumab monthly arm and 31-to-41-percent reduction in the eyes originally assigned to ranibizumab and bevacizumab PRN arms, respectively. The drop in vision in conjunction with increased bevacizumab use on a less-frequent dosing regimen would confer greater evidence as to the inferiority seen at two years in the bevacizumab PRN arm compared to monthly ranibizumab.

In our FIDO study published last year, patients achieved visual acuity gains with continuous dosing over seven years.[13] In this retrospective study, we identified 44 eyes with at least seven years of consistent treatment with continuous, fixed-interval dosing between four and eight weeks. This provided a unique data set to explore the effect of prolonged continuous exposure to anti-VEGF therapy in wet AMD.

Similar to the previously mentioned studies, our cohort demonstrated significant visual gains that peaked at year two (+16.1 letters). Between years two and seven, a trend toward a 0.8-letter/year decline emerged, with an overall 12.1-letter gain from baseline at seven years (*Figure 2*). The percentage of patients maintaining driving vision at seven years was comparable to Dr. Gillies' study at 43.2 percent compared to the 23 percent SEVEN-UP reported.[12,14]

So Why Fewer Injections?

The basic tenet of continuous, fixed-interval dosing is to maintain therapeutic levels of VEGF suppression to prevent new vessel formation, leakage, bleeding and fibrosis. The three studies with seven-year data demonstrated a direct correlation between number of injections and visual acuities (*Table*). So if short-term and long-term data point toward improved outcomes with more rigorous injection schedules, then why is there a trend toward fewer injections?

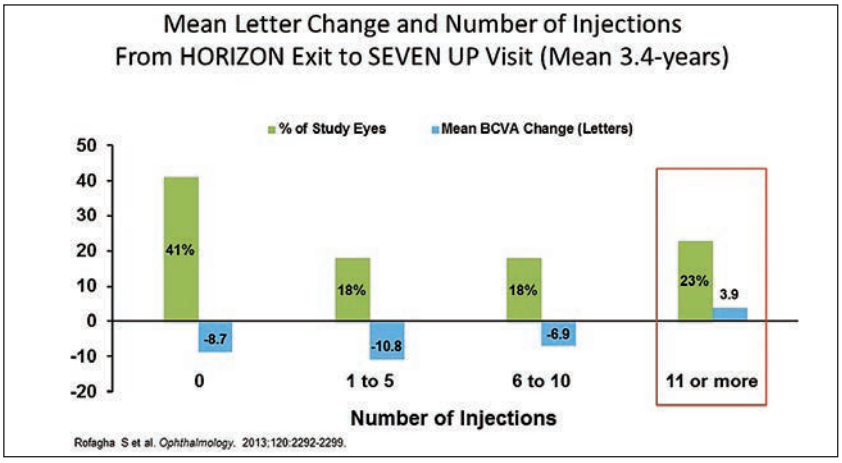

Figure 3. This bar graph shows mean letter change based upon number of injections received after exiting HORIZON. Patients in the highest quartile (11 or more injections) maintained visual acuity better than baseline.

The answer is complex and multifactorial, but one can certainly cite the burden of frequent visits and treatment to practices, patients and families. In fact, the most recent American Society of Retina Specialists preferences and trends (PAT) survey found that 47 percent of physicians felt it was due to both them and patients preferring less-frequent dosing even at the risk of decreased visual acuity.[16]

Perhaps more importantly, we must acknowledge that these injections come with a cost and an inherent risk to the patient when we consider complications such as endophthalmitis and retinal detachment. But are there other risks that treating physicians are worried about?

While VEGF can lead to the deleterious effects seen with choroidal neovascular complex formation, it is neurotrophic for retinal photoreceptors and retinal pigment epithelium cells. Indeed, VEGF-A knock-out mice demonstrated progressive atrophy of the choriocapillaris with ensuing photoreceptor dysfunction and loss.[17] Subanalyses from CATT reported a 1.59 greater risk of geographic atrophy (GA) in eyes receiving monthly therapy compared to PRN.[8] Other studies have confirmed atrophy, with 89.7 percent demonstrating central atrophy in SEVEN-UP, but Dr. Gillies' study attributed only 37 percent of vision loss to central atrophy.[12,14]

Despite the increased prevalence

Table. Letter Changes and Injections/Year for Long-term Seven-year Studies

Seven-Year Results	FIDO	SEVEN-UP	Gillies et al.
Mean [delta] Vision	+12.1 letters	-8.6 letters	-2.6 letters
Mean Treatments/Year	10.5 injections	1.6 injections*	Five injections

*Average over one to four years after exit from HORIZON trial

of atrophy in patients receiving more sustained VEGF suppression, we cannot infer a direct causation. A recent study by Miho Tanaka, MD, and colleagues demonstrated that after 3.5 years, GA did not tend to occur outside the boundaries of the initial choroidal neovascularization (CNV) unless the eyes had GA outside this area at baseline.[18] Subsequent analysis of the CATT study data also seemed to refute a direct causation between increased VEGF suppression and GA.

Despite the increased prevalence of GA reported in the initial study, the rates of growth were nearly identical at 0.43 mm per year and 0.44 mm per year in the PRN and monthly groups, respectively.[19] Giovanni Staurenghi, MD, performed another analysis of the data that pointed toward the increased prevalence of patients with reticular pseudodrusen and retinal angiomatous proliferation in the subgroups that had a higher incidence of GA.[20] These particular wet AMD phenotypes have been associated with higher risk toward development of GA and may have affected the original conclusions as well.

The GA controversy is certainly not over. The ASRS PAT survey reported that 31 percent retina specialists still believe that anti-VEGF causes macular atrophy and an additional 40 percent are unsure of the relationship.[16]

A recent publication may help alleviate some of this concern. The SEVEN-UP fellow-eye study looked at prevalence and growth of GA in both study eyes and fellow eyes.[21] Patients initially enrolled in the ANCHOR and MARINA trials were ineligible for treatment in the fellow eye, allowing for a natural progression comparison. After seven years, macular atrophy progression was more severe in the fellow eyes that were exudative at baseline, while fellow eyes that remained non-exudative showed the least amount of atrophy.

Comparisons between eyes of individual patients demonstrated a mean change in area of 4.1 mm^2 in those fellow eyes that were exudative at baseline and left untreated for two years, while the study eyes showed a mean increase of only 2.2 mm^2. These findings give credence to the hypothesis that continuous exposure of photoreceptors and RPE cells to subretinal fluid, intraretinal fluid and blood may accelerate the progression of atrophy, contradicting concerns of the two-year CATT data and suggesting that continuous anti-VEGF treatment may actually be protective and reduce the rate of progression of macular atrophy in the long term.

Where Do We Go From Here?

While available long-term data is limited in that it is retrospective, the preponderance of evidence points toward improved outcomes with sustained exposure to anti-VEGF agents in patients with wet AMD. With new data suggesting that such therapy may actually delay the progression of GA, the groundwork for the benefit of sustained-release delivery of these agents has been laid.

How we will use these agents with novel pharmacologics is an exciting prospect for retina specialists and our patients. Perhaps by limiting fibrosis with anti-platelet derived growth factor agents, we may also observe a delay in the progression of atrophy. What's more, while atrophy seems to be an inevitable process in both exudative and non-exudative AMD, perhaps combined therapy with complement inhibitors will further reduce progression. Only the future will tell, but in the meantime, treat early and often with VEGF inhibitors. RS

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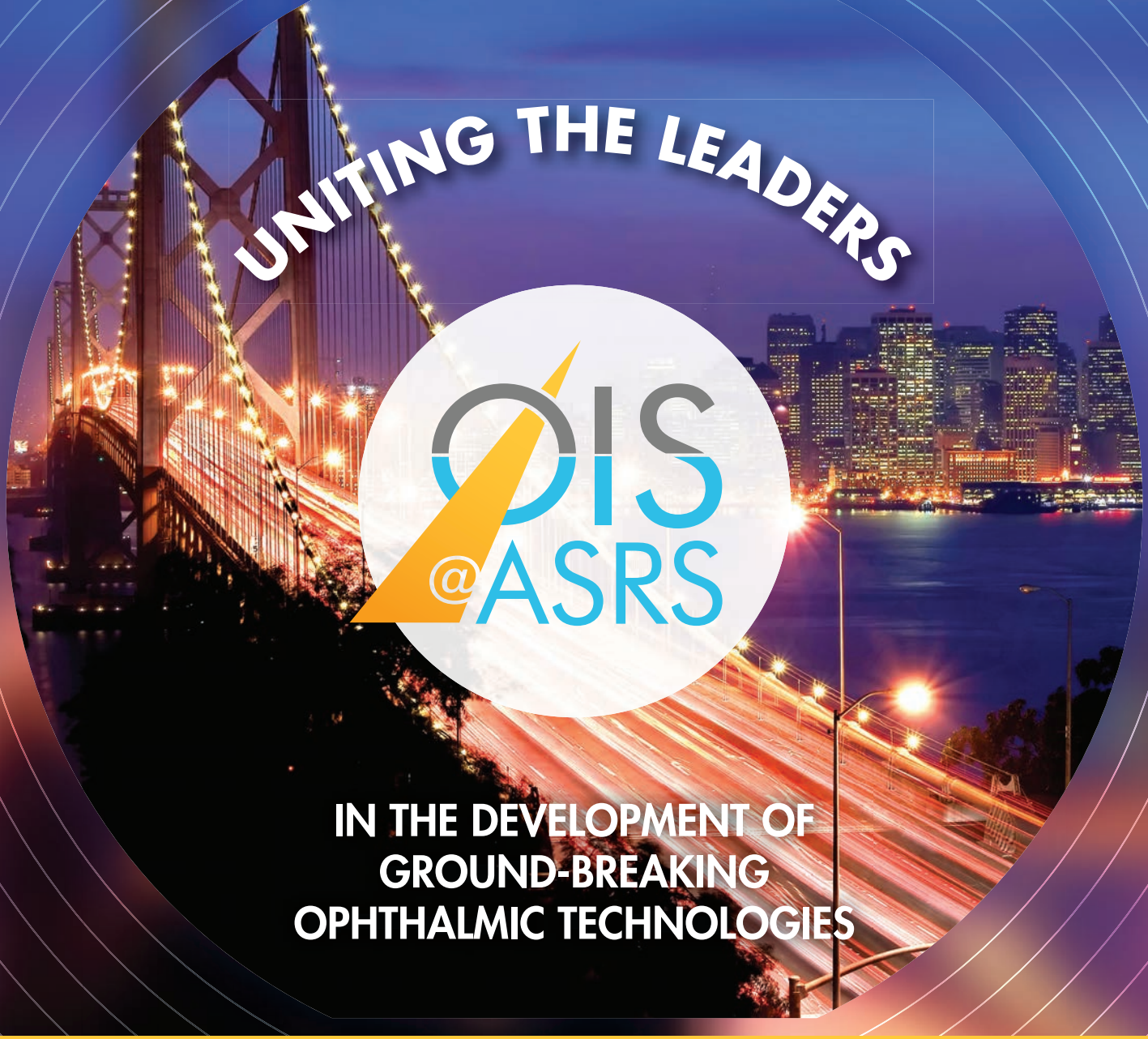

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DRCRNET PROTOCOL T 2-YEAR DATA: WHERE DO WE GO FROM HERE?

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

By Carl Baker, MD

The toll of diabetic retinopathy has been well documented: Approximately 750,000 people in the United States over the age of 40 have diabetic macular edema, and it continues to be a leading cause of vision loss in the United States.[1] For decades we relied on macular laser treatment to reduce vision loss from DME, but in the past eight years an abundance of evidence has been building to support the use of intravitreal anti-VEGF agents as a primary treatment of DME.

However, many questions still need to be answered regarding anti-VEGF injections for DME, among them:

- Which anti-VEGF agent is most effective?
- How many injections are required?
- What role does laser play in DME management?
- Which drug is most cost effective?
- How safe is anti-VEGF treatment?

The Diabetic Retinopathy Clinical Research Network (DRCRnet) has been a leading enterprise in clinical research on diabetic retinopathy and, specifically, DME. Over the last decade, DRCRnet Protocol I evaluated ranibizumab (0.5 mg) (Lucentis, Genentech) injections vs. the "gold standard" macular photocoagulation for the treatment of DME.[2] The findings of DRCRnet Protocol I clearly demonstrated superiority of ranibizumab with prompt and deferred focal laser over laser treatment alone.

The visual benefits from anti-VEGF injections for DME seen in Protocol I had been maintained through five years of follow-up.[3] Subsequent clinical trials[4,5] have demonstrated that bevacizumab (Avastin, Genentech) reduced vision loss due to DME, and industry-sponsored trials also found strong evidence to support the use of both ranibizumab and aflibercept (Eylea, Regeneron Pharmaceuticals) in the treatment of DME.[6-10]

Protocol T: Which Works Best?

To expand the knowledge base regarding effectiveness and anti-VEGF treatment strategies, the DRCRnet designed Protocol T to compare the efficacy of ranibizumab, aflibercept and bevacizumab for the treatment of DME.[11] The study recruited 660 subjects with decreased vision and DME from 89 community-based and academic practices.

The study randomized the

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Disclosure: Dr. Baker performs research with Genentech, Regeneron, Alcon, Allergan, Ophthotech, Alimera, Iconic, Thrombogenics, Glaxo-Smith-Kline and Acucela, and has served on an advisory board for Roche.

enrolled eyes into three groups receiving injections of bevacizumab (1.25 mg), ranibizumab (0.3 mg) or aflibercept (2 mg). The subjects were evaluated and treated by the standard DRCRnet anti-VEGF algorithm based on changes in visual acuity and macular thickening on optical coherence tomography. Although the study was not powered to compare safety outcomes, it did collect safety data, including ocular adverse events and systemic adverse events.

Primary outcome results at one year were published in the *New England Journal of Medicine*.[12] A treatment course with all three drugs resulted in significantly improved visual acuity. Aflibercept resulted in the largest mean improvement of vision (18.9 letters) with ranibizumab (14.2) and bevacizumab (11.8) having less improvement at one year. The statistical difference between the acuity improvements was driven by the enrolled eyes with 20/50 or worse baseline vision. This division of the cohorts was a pre-specified analysis done by the DRCR network. Approximately half of the subjects in Protocol T had 20/40 or better vision at baseline, and these eyes showed no difference in vision outcomes between the three drugs.

The Protocol T two-year data provide longer-term evidence that anti-VEGF therapy is efficacious in treating DME. In many ways, the two-year findings are similar to the one-year results. The most significant development in the two-year data dealt with the visual acuity results. At two years, the superior visual results of aflibercept over ranibizumab, documented at one year, were no longer present.[13] The only statistical difference in acuity among the three drugs after two years was aflibercept's superiority to bevacizumab in eyes with 20/50 or worse baseline vision. Over two years, when the baseline visual acuity was 20/40 or better, no significant visual acuity outcome differences between the three drugs were noted.

Seven Takeaways from Two-year Protocol T Results

1. All three drugs resulted in visual acuity improvements through two years of treatment.
2. When baseline visual acuity was 20/40 or better, visual improvement was similar between all three treatments.
3. Throughout the study, eyes with baseline visual acuity of 20/50 or worse had less vision improvement with bevacizumab.
4. Aflibercept's superiority to ranibizumab at one year was no longer present in the two-year results.
5. Eyes treated with aflibercept required fewer macular laser treatments during the two years of the study.
6. The number of injections required for all three drugs using the DRCRnet treatment protocol was approximately 10 in the first year and five in the second year of treatment.
7. Throughout the trial, bevacizumab treatment resulted in less improvement in thickening as measured with optical coherence tomography compared with the other two drugs, although the differences were less pronounced at two years.

How Many Injections?

The DRCRnet anti-VEGF injection treatment algorithm consists of a monthly evaluation and dosing schedule with criteria for injection deferral depending on visual acuity changes and OCT measurements. This differs from other clinical trials where the dosing schedule was fixed throughout the course.[8,9]

The Protocol T treatment algorithm allowed for some reduction in the need for injections over time and provided an opportunity to see if any of the three drugs required fewer injections over a two-year treatment course.[11] Because investigators were not masked to the treatment intervention in Protocol T, strict OCT and visual parameters were necessary to minimize investigator discretion and potential bias throughout the trial.

Protocol T follow-up showed no significant differences in the number of intravitreal injections each of the three treatment groups required, with 15 to 16 injections over the full two years and five to six in the second year alone.[13] The observed reduction in the need for anti-VEGF treatment for DME was consistent with results from Protocol I.[3]

Certainly, there have been clinical reports of visual outcomes that were inferior to the clinical trials.[14] In many cases this may be due to undertreatment or lack of adherence to an appropriate dosing program. More than 80 percent of respondents to

Take-home Point

Long-term results from both DRCRnet Protocol I and Protocol T have demonstrated sustained visual acuity improvements using anti-VEGF treatment and a substantially decreased need for additional anti-VEGF injections in subsequent years of treatment. For best visual results, diabetic macular edema requires aggressive treatment initially (approximately 10 injections in year one) with continued benefits from less frequent injections in later years.

the American Society of Retinal Specialists Preferences and Trends survey indicated that they consider alternate treatment for DME after five injections or less.[15] A recent publication from the Pan-American Collaborative Retina Study reports the initial visual benefits from bevacizumab for DME were not sustained over five years.[16] However, those study eyes only received a mean of 8.4 injections over five years, which is about half the injections that Protocol T eyes received over two years.

The DRCRnet algorithm is not truly a "treat-and-extend" or PRN dosing regimen, so some clinicians have had difficulty in adopting it. The DRCRnet has attempted to clarify its treatment algorithm through publications and programs at meetings (*Figure*).[17]

The simplified algorithm is as follows: Once treatment with anti-VEGF injections has started, retreat every four weeks until vision and OCT are stable for two consecutive visits; after deferring injections, re-treatment begins again if edema returns or vision worsens. Even when DME is chronically persistent, the DRCRnet treatment algorithm has been shown to result in stable visual results.[18]

Role of Laser

The Protocol T treatment algorithm included macular photocoagulation if, after six months of anti-VEGF treatment, DME was persistent and not improving. Additional laser treatments were permitted 13 weeks after the last laser if the DME continued to persist and untreated microaneurysms associated with the edema were present. The protocol discouraged macular photocoagulation closer than 500 µm from the macular center.

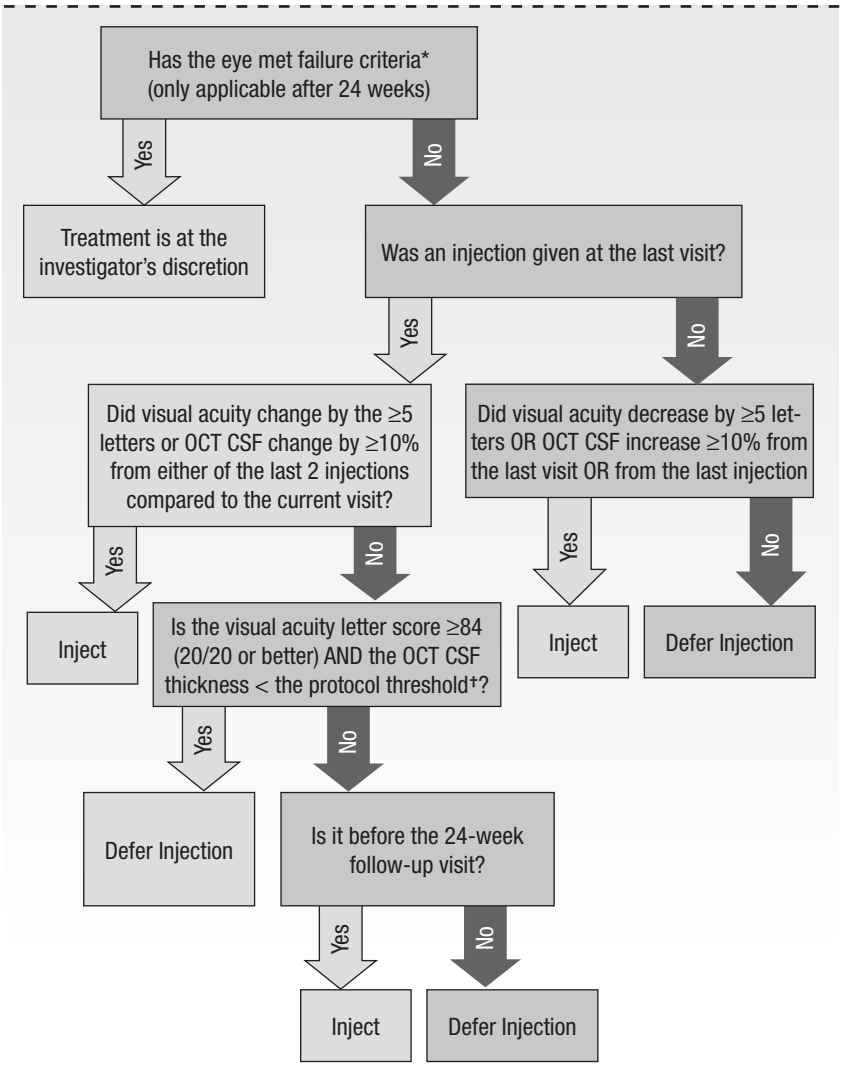

Figure. Diabetic macular edema treatment with anti-VEFG during follow-up. OCT = optical coherence tomography, CSF = central subfield, DME = diabetic macular edema *Failure = failure can only be met at or after the 24-week visit IF each of the following are met: A) OCT CSF thickness ≥ eligibility threshold; B) visual acuity is 10 or more letters worse than baseline at two consecutive visits; C) DME present on clinical exam that the investigator believes is the cause of the visual acuity loss; D) complete focal/grid laser for DME has been given; E) there has been no improvement in visual acuity (>5 letters) or OCT (>10% OCT CSF thickness) since either of the last two injections; F) there has been no improvement in visual acuity (>5 letters) or OCT (>10% OCT CSF thickness) since the last focal/grid laser treatment for DME was given; and G) it has been ≥13 weeks since the last focal/grid laser treatment for DME. †Protocol threshold = >250 µm on Zeiss Stratus; ≥ 320 for men or ≥305 for women on Heidelberg Spectralis; ≥305 for men or ≥290 for women on Zeiss Cirrus.
Used with permission of Massachusetts Medical Society.

Over the two years of Protocol T, fewer eyes treated with aflibercept required macular photocoagulation; 41 percent received at least one ses-

sion of focal/grid photocoagulation, vs. 52 and 64 percent for ranibizumab and bevacizumab, respectively.[13]

Which Is Most Cost Effective?

The three drugs studied in Protocol T have significantly differing costs. The approximate costs derived from Medicare is $1,950 per dose for aflibercept, $1,200 for ranibizumab (0.3 mg) and $50 for bevacizumab.[12] The results from both years one and two of Protocol T suggest that patients with 20/40 vision or better at treatment initiation will have a similarly good chance at visual improvement with any of the three drugs.

In eyes with 20/50 or worse initial vision, aflibercept and ranibizumab may lead to a more substantial improvement in vision but have significant incremental costs over the use of bevacizumab. The cost analysis method of quality-adjusted life-years (QALY) analysis[19] suggested the value of bevacizumab as a treatment for DME is substantially greater than ranibizumab or aflibercept even in eyes that benefit most from the more expensive drugs. Cost-effectiveness analyses on Protocol T results suggest that the cost of aflibercept and ranibizumab would need to be reduced by 65 to 85 percent to have similar value to bevacizumab for DME treatment.[20]

How Safe Is Anti-VEGF?

The incidence of adverse events in all three groups of Protocol T was consistent with previously reported safety results from major clinical trials.[13] Pre-specified adverse events, including deaths and hospitalizations, were comparable between the three groups. Vascular adverse events, as defined by the Antiplatelet Trialists' Collaboration (APTC),[21] occurred more frequently in the ranibizumab group (12 percent vs. 8 percent for bevacizumab and 5 percent for aflibercept; p=0.047).[13] This finding is not consistent with previous clinical trial data, especially the RISE study and DRCRnet Protocol I, in which ranibizumab treatment was associated with a lower risk of APTC events compared with control groups. Overall, intravitreal use of anti-VEGF agents has not been shown to be associated with overall mortality, cardiovascular mortality, hypertension or stroke.[22]

The rates of ocular adverse events were low in all three groups. One case of endophthalmitis was reported in more than 9,000 injections throughout the course of the trial. The rate of retinal tears and detachments (including tractional detachments) was less than 1 percent in each group. A rise in IOP, defined as an increase of 10 mm Hg of more from baseline, 30 mm Hg or greater at any visit or initiation of glaucoma medications or glaucoma surgery, was noted in 15 percent of the Protocol T patients.[13] This will likely be an aspect of anti-VEGF injections that will receive further investigation.

Another safety issue concerns bevacizumab repackaging. The bevacizumab used in Protocol T was repackaged centrally and tested for sterility and potency into glass containers similar to those used to package the commercially available aflibercept and ranibizumab.[12] However, in clinical practice the available supply of bevacizumab is generally packaged differently, often into plastic syringes, and may be less consistently safe and potent than that used in Protocol T.[14,23] Although the rates of endophthalmitis associated with bevacizumab appear to be similar to commercially available ranibizumab and aflibercept,[24] there have been reports of less potency in bevacizumab in plastic syringes.[25] Decreased potency may cause inferior efficacy with bevacizumab.

Conclusion

Protocol T demonstrated anti-VEGF injections are an effective treatment for DME. When visual impairment is mild, all three commercially available anti-VEGF drugs improve visual acuity. In eyes that have moderate to severe visual impairment, ranibizumab and aflibercept have been shown to lead to the most visual improvement.

The cost of bevacizumab enhances its value in the management of DME compared to the other anti-VEGF agents. However, the safety and reliable potency of compounded bevacizumab may limit its utilization. Reduced anti-VEGF dosing is common in clinical practice, but lesser dosing than the DRCRnet algorithm may result in less visual improvement.

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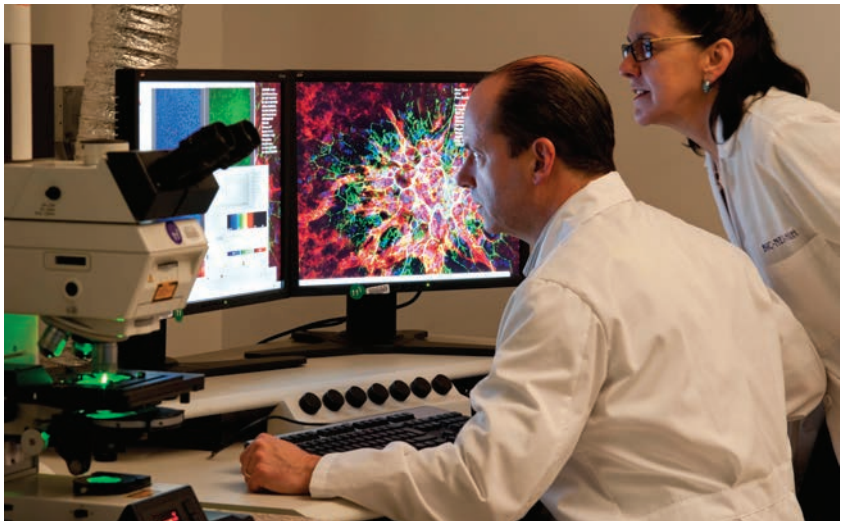
(Continued on page 46)

RETINA REPORT FROM ARVO 2016

A closer look at five abstracts on VMT, DME, AMD, OCT and gene therapy.

By Ashkan M. Abbey, MD

The field of retina continues to evolve and advance rapidly through the work of outstanding researchers from the laboratory bench to the bedside. Here, we present five compelling posters and presentations from ARVO 2016 in Seattle. They include a comparative trial of various treatments for symptomatic vitreomacular traction (VMT); a new subcutaneous treatment for diabetic macular edema (DME); topical dorzolamide-timolol for neovascular age-related macular degeneration; exciting progress in retinal gene therapy; and new insights and applications of optical coherence tomography angiography.



After each abstract, you will find a citation representing the abstract number, which you can use to locate the original report. Disclosures are also noted.

Treatment of VMT

Intravitreal injection of C3F8 gas demonstrated superior release rates for symptomatic VMT when compared to both intravitreal injections of SF6 gas and ocriplasmin (Jetrea, ThromboGenics). One hundred thirteen consecutive patients with VMT were treated with one of three interventions: 0.25 mL of 100% C3F8 gas (32 patients); 0.25 mL of 100% SF6 gas (27 patients); and 0.1 mL of ocriplasmin (54 patients). Patients who received gas injections were instructed to perform "drinking bird" head movements, in which they would bob their head forward

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Disclosure: Dr. Abbey disclosed he is a consultant for Allergan.

and backward two to three times every hour for the first few days after injection.

The VMT release rate after follow-up beyond six months was 84 percent (27/32) with C3F8, 56 percent with SF6 and 48 percent with ocriplasmin. Furthermore, the patients receiving gas were characterized as having "mobile" vs. "taut" VMT by live dynamic OCT imaging during horizontal and vertical voluntary saccades.

"Mobile" VMT released more frequently than "taut" VMT with gas injection ($p<0.05$). No retinal breaks occurred in this series. One investigator disclosed a relationship with ThromboGenics.[1806]

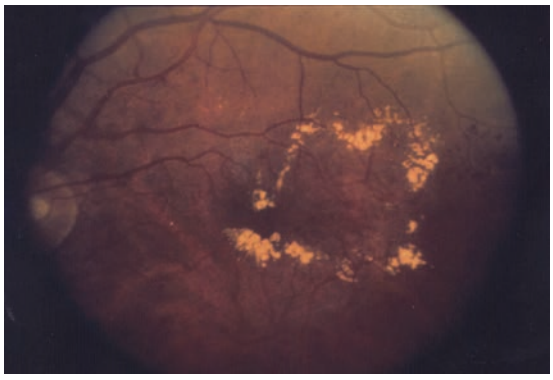
Systemic Treatment for DME

The subcutaneous injection of AKB-9778 (Aerpio Therapeutics), a Tie2 activator, in combination with intravitreal injections of 0.3-mg ranibizumab (Lucentis, Genentech), enhances reduction of DME compared to ranibizumab monotherapy. Tie2 is a receptor tyrosine kinase expressed almost exclusively in endothelial cells that becomes deactivated in diabetic patients, leading to increased vascular permeability and leakage. AKB-9778 inhibits vascular endothelial-protein tyrosine phosphatase (VE-PTP), the most critical negative downregulator of Tie2.

In this randomized, double-masked, double-dummy trial of DME patients with OCT central subfield thickness (CST) of 325 µm or greater, the participants were randomized into three groups:

- Subcutaneous AKB-9778 plus monthly sham intravitreal injection.
- Subcutaneous AKB-9778 plus monthly intravitreal 0.3-mg ranibizumab (combination group).
- Subcutaneous placebo plus monthly intravitreal 0.3-mg ranibizumab (monotherapy group).

At three months, there was a statistically significant difference in reduction of CST between the combination treatment group and the ranibizumab monotherapy group (-163.8 ±24.3 µm vs. -109.2 ±17.2 µm, $p=0.008$). In the combination group, fellow eyes demonstrated improvement in diabetic retinopathy severity score that was equivalent to the treatment eyes. There were no treatment group differences in adverse events.



This study demonstrated the enhanced effect of anti-VEGF therapy on DME with a well-tolerated subcutaneous medication. In addition to its benefits on the fellow eye, AKB-9778 may have further unrealized potential in the risk modification of other systemic diabetic complications related to microangiopathy, such as kidney disease. The study author disclosed a relationship with Aerpio Therapeutics.[2319]

Dorzolamide-Timolol for AMD

Topical dorzolamide-timolol appears to reduce subretinal fluid and CST in eyes with persistent exudation related to neovascular AMD despite consistent, fixed-interval intravitreal injections of anti-VEGF medication. This prospective study involved 10 eyes with persistent macular edema despite fixed-interval intravitreal anti-VEGF injections (mean of 21.9 prior injections). Eight eyes received aflibercept (Eylea, Regeneron Pharmaceuticals) and two were treated with ranibizumab. The enrolled patients received twice-daily topical dorzolamide-timolol in the treatment eye while continuing their previous regimen of intravitreal injections. Patients were followed for at least two visits after enrollment.

The study reported significant reduction in mean CST, from 419.7 µm at enrollment to 334.1 µm at the final visit ($p = .01$). Mean maximum subretinal fluid height decreased from 126.6 µm at enrollment to 49.5 µm at the final visit ($p = .02$). LogMAR visual acuity improved from 0.54 at enrollment to 0.48 at the final visit ($p = .60$).

This study suggests that topical dorzolamide-timolol may be an easily administered and effective topical adjuvant therapy for recal-

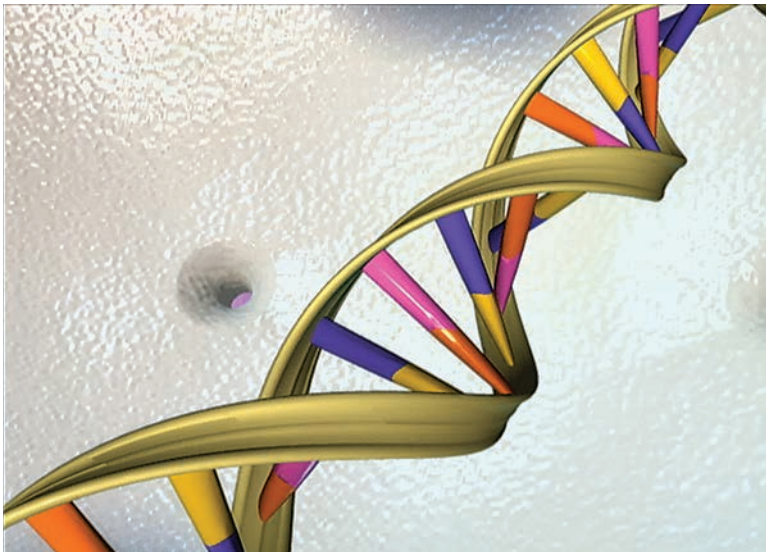
Take-home Point

This deep dive into five ARVO 2016 presentations looks at the use of C3F8 gas in vitreomacular traction, results of a Tie2 activator in combination with intravitreal injections for diabetic macular edema, use of topical dorzolamide-timolol to reduce subretinal fluid and central subfield thickness, gene therapy with adeno-associated viral vectors for choroideremia and measurement of choroidal neovascular membrane area with optical coherence tomography angiography.

citrant neovascular AMD. Larger, controlled studies will be useful to validate these intriguing findings. The authors had no relevant disclosures.[4441;Poster #A0346]

Retinal Gene Therapy

Choroideremia is an X-linked recessive chorioretinal dystrophy caused by loss-of-function mutations in the gene CHM, generally leading to significant central vision loss



in the fourth or fifth decade of life. A recent clinical trial in the United Kingdom utilizing gene therapy with adeno-associated viral (AAV) vectors for choroideremia showed sustained visual benefits in five out of six patients after 3.5 years of follow-up.

A subretinal injection of an AAV vector encoding the choroideremia gene was performed after vitrectomy in six eyes. Five eyes received a dose of 1,010 genome particles, and one eye received a dose of 6 x 109. The fellow eye was left untreated as a control in all six patients.

After 3.5 years, visual acuity change in the five eyes treated with the higher dose was +8.4 ± 4.7 letters in the treated eyes and -8.8 ± 3.1 letters in the control eyes, equivalent to a mean difference of more than three lines. The eye that received a reduced dose demonstrated a steady decline in vision over the follow-up interval.

Overall, two eyes demonstrated sustained improvements in vision, while three other eyes maintained their baseline vision despite losing vision in the fellow control eyes over 3.5 years. The encouraging outcomes from this small trial may provide a basis for gene therapy for a number of retinal diseases in the future. Several authors disclosed a relationship with Nightstarx Ltd.[2297]

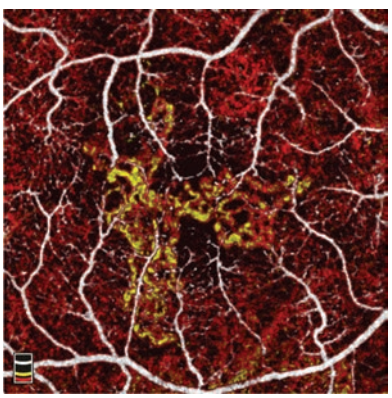
OCT Angiography

Choroidal neovascular (CNV) membrane area can be automatically measured with OCT angiography (RTVue-XR, Avanti, Optovue) using a saliency-based algorithm with excellent repeatability. In a small, prospective study, seven treatment-naïve patients with CNV due to neovascular AMD underwent OCT angiography scans at baseline and monthly visits while being treated on a PRN basis with anti-VEGF medication. Six of seven eyes showed initial reduction in CNV area over the course of three anti-VEGF injections, demonstrating its utility in monitoring treatment response.

In one case, CNV area decreased with treatments, then remained stable without treatment after resolution of subretinal fluid. Another patient was noted to have a reduction in CNV area and complete resolution after three monthly anti-VEGF treatments.

However, after three months of observation, the CNV area increased without the presence of fluid on OCT. One month later, the eye developed subretinal fluid requiring treatment. This suggests that CNV growth on OCT angiography may precede the recurrence of fluid on structural OCT.

The measurement of CNV area using OCT angiography provides potentially useful clinical applications of this new imaging modality in patients with CNV. Although further study is needed, the increase in CNV size may serve as an earlier indicator of the need for treatment in these patients. Several authors disclosed relationships with Optovue.[2162;Poster #D0008]



Argus II in the Real World

Experience with six patients who have had this device implanted. ***By Joshua Manusow, MD FRCSC, Robert Devenyi, MD, FRCSC, Samuel Markowitz, MD FRCSC, Michelle Markowitz, OD, MSc. OT, and Nicole McLaren, OA***

Editor's Note: In this new department, Efrem D. Mandelcorn, MD, FRCSC, of Toronto Western Hospital of the University of Toronto University Health Network, shares ex-United States clinical perspectives from Canadian retina colleagues.

Restoring useful, functional vision to patients with previously untreatable retinal diseases is a dream that is becoming a reality. Though in its infancy, the use of retinal prostheses to treat patients blinded by outer retinal degenerations is being performed in specialized centers.

At Toronto Western Hospital (TWH), we were the first team in Canada to implant the Argus II Retinal Prosthesis (Second Sight Medical Products) in patients with outer retinal degenerations. Our first patient had surgery in the summer of 2014. Since then we have implanted five additional patients. Here, we share what we've learned so far about this device and patient expectations.

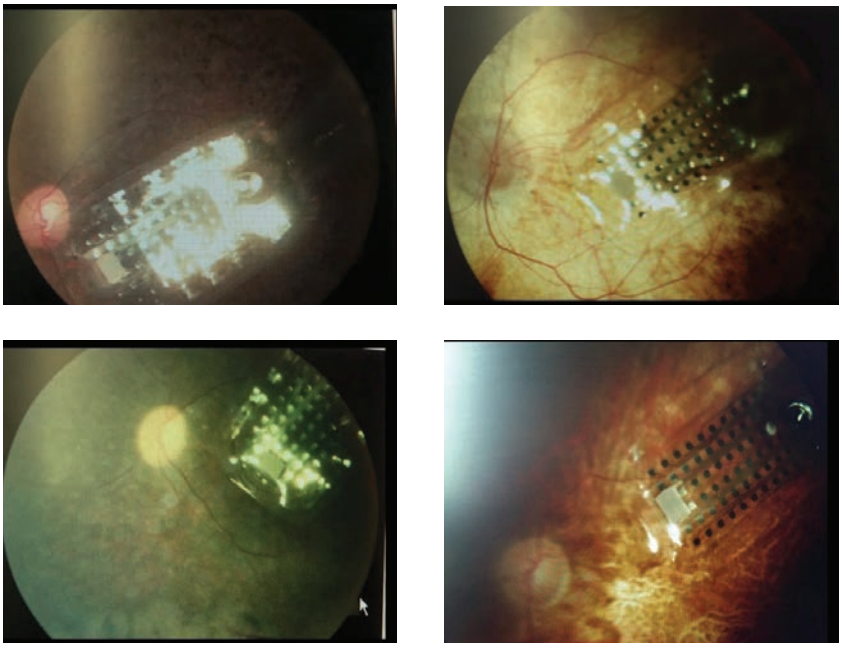


Figure. Fundus photographs showing the array sitting on the macula in four of our first five Argus II patients.

What It Is and How It Works

The Argus II is an epiretinal prosthesis designed to electrically stimulate the visual system by bypassing the outer retina. Its goal is to provide these patients with an improvement in their functional vision.

The Argus II system consists of two components: an eyeglass-mounted camera connected to a video processor and battery unit worn on a belt; and an ocular component consisting of a receiving/transmitting coil, electronics case and a 60-electrode array. The array is implanted in an epiretinal location and is secured to the macula using a retinal tack (*Figure*). It is connected to the electronics housing via a ribbon cable inserted through a 5-mm pars plana incision. The electronics housing is secured to the sclera and is flanked by a receiving coil that sits on a band implanted under the rectus muscles like a scleral buckle.

The camera on the glasses captures an image and sends it to the video processor worn on the belt clip. The processor converts the image into pixels that can stimulate the 60-electrode array. This image is then sent back to the glasses where it is wirelessly transmitted to the receiver coil on the encircling band.

The signal is sent through the electronics housing and down the transmitting coil to the epiretinal array sitting on the macula. The electrodes on the array stimulate the functional inner retina and the signal is sent down the usual visual pathway, thus bypassing the outer retina. The patient perceives an image made up of a combination of 60 phosphenes, or points of light.

The Implant Operation

The surgical steps involved in implantation are familiar to most retinal surgeons. It is similar to performing a scleral buckle, vitrectomy and glaucoma valve.

The surgery begins like any

scleral buckling procedure with conjunctival peritomy and isolation of the rectus muscles.

Next, the receiver coil is centered underneath the lateral rectus and the electronics package placed in the superotemporal quadrant and secured with sutures similar to placing a glaucoma valve. The encircling band is placed under the remaining recti and secured with a standard sleeve.

A core and peripheral vitrectomy is performed. A 5-mm pars plana incision is made in the superotemporal quadrant with a microvitreoretinal blade. The precise location of this incision is calculated based on the anatomy and axial length of the eye. The goal is for the array to lie precisely over the macula, with no twisting or tension of the ribbon cable that connects the array to the electronics box.

The array is introduced into the vitreous cavity through the incision. It is tacked to the macula with a retinal tack, which is essentially a sharp miniature tack introduced through the array, retina, choroid and sclera. An engineering team tests the impedance of each electrode intraoperatively. The electronics package and receiver coil are covered by donor pericardium to prevent conjunctival erosion. The eye is closed and the procedure is over.

The Rehabilitation Process

The rehabilitation team begins programming and basic training at postoperative week one. The team creates customized thresholds to ensure that electric current produces a comfortably bright spot of light for the patient. The patient learns basic functions like turning the system on and choosing between different modes. More importantly, the patient learns the minimal skills necessary to enable the system to produce a meaningful image; that is, eye movement and precept localization awareness, eye position and radio frequency link awareness, and head-scanning behavior.

Following basic training, the patient can begin to start practicing at home. The patient meets with our team to practice and learn the six essential skills: eye, head and camera position awareness and movement; small-scale light localization (microscanning); large-scale light localization (macroscanning); tracking; luminance discrimination; and shape recognition.

The most important part of visual rehabilitation is setting realistic goals. The Argus II is a low-vision device, a 10-by-6 array that can provide a 20-degree field of vision. Patients who expect the device to restore "normal vision" will always be disappointed. Argus II is unlike any other low-vision tool in that it can improve activities of daily living and assist in orientation and mobility. Selecting patients who understand that, and setting appropriate goals before and after surgery, are keys to a successful outcome.

The Canadian Perspective

To our knowledge, TWH is the only site in Canada with experience in providing the Argus II to multiple patients. Our team consists of the surgeon, fellows and residents, surgical nurses, rehabilitation ophthalmologists and optometrists, surgical coordinators, engineers from Second Sight, our hospital foundation and the families of patients. We have funding to provide a total of 10 Argus II devices from a donor through our hospital foundation.

The price of the implant alone is more than $107,000 U.S. and $140,000 Canadian. We hope that one day our provincial health-care system will cover it. We screen patients from all over Canada who are 25 years old and older, have severe to profound retinitis pigmentosa, bare light perception or no light perception with a functional inner retina, and have a history of prior useful form vision.

Variable Patient Results

Our results have been variable. Some patients describe it as a life-changing experience and even, remarkably, say they are able to read some letters on the eye chart. Others no longer use the device. Our younger patients seem to be doing better with the new technology. Approximately one-third of our patients are very happy, one-third somewhat happy and one-third less so. We are getting better at predicting who will do well with this technology and we hope to have even happier patients as our understanding of patient selection improves.

There is certainly a learning curve with any new, state-of-the art technology. We have found the Argus II to be a challenging, exciting and worthwhile experience. The idea of giving useful vision back to someone with no-light-perception vision seems like science fiction, but it is happening in Toronto. We are grateful to be involved and excited to see what we can achieve for patients that we, as vitreoretinal surgeons, once had nothing to offer.

The authors are with the University of Toronto Department of Ophthalmology and Vision Sciences, University Health Network/Toronto Western Hospital Department of Ophthalmology.

Is a Billing Service the Right Move?

It's a way to outsource accounts receivable management, but it's not the right decision for every practice. ***By Kari Rasmussen***

Accounts receivable management for retina practices is one of the more complex in medicine due to a great extent the extensive use of high-cost biologics. So, it may be worth looking at switching your accounts receivable (AR) management from in-house to a billing service.

What are the motivating factors steering you toward this decision? Among the reasons practices cite are cost savings, challenges with finding and/or retaining qualified staff and a reduction in operational costs.

Questions and Considerations

How much do billing services charge? Generally billing services base their charges on a percent of collections. Be sure to evaluate the service charge on high-cost biologics to ensure you are made whole.

Not all billing services offer the same services, or even the same level of services, so vet them carefully. Since the employees of the billing service will be interacting with your patients, they become a direct extension of your practice. Does the billing service reflect the culture you wish to portray?

Other considerations include:

- Does the service have expertise in retina billing?
- Will it assign staff dedicated to your account?
- Is the service familiar with programs like Good Days or Patient Access Network Foundation/CoreSource and what its role would be in working with these programs?
- Who will obtain prior authorizations: the service or your staff?
- Can the service integrate with your electronic health records (EHR) and/or scheduling programs?
- What about termination? Who keeps the AR and collect-out?
- Will you maintain the ability to continue to audit your AR?
- How will your existing AR be handled?

Personnel Issues

Existing staff may resist the idea of an outside billing service, and management must also get on board to ensure an smooth transition. You will also need to have an internal point person to address myriad needs between the offices—copies of medical records, assistance with appeals, confirmation of treatments and questions or concerns patients may have.

Our practice has considered using a billing service on several occasions. We have two full-time individuals who handle all aspects of our AR management. To keep up with all the prior authorizations and applications for financial assistance, we determined we would still have to maintain at least a part-time position. When considering all the factors I have outlined here, making a switch was cost-prohibitive for our practice.

Transferring the burden of recruitment, training and retention of quality employees to a billing service can help considerably. This is an important consideration if your present billing staff consists of one to three employees. You run the risk of losing important institutional knowledge should one of these individuals leave.

Where It Can Make Sense

However, practices in large, metropolitan areas, where salaries and real estate costs are considerably higher, find that switching to a billing service results in significant savings. Don Shay, previously administrator for Retina Consultants of Houston, says, "We can now use the office space that was once occupied by the billing department for other purposes, such as research, diagnostics and exam rooms."

A billing service may be a great option for a start-up practice, too, because it can provide all the credentialing, contract review and negotiations, fee-ticket creation and integration with scheduling and EHR, thus allowing the doctor to focus on building the clinical aspects of the practice.

Finding Lost Money

Billing services may be able find underpaid claims, charges written off in error or claims that should be appealed or rebilled that otherwise would have been missed. "We manufacture money," Ryan Patano, vice president of Alta Medical Management, a billing service in Salt Lake City, tells me. "Our job is to get physicians paid more money, more quickly, with higher patient satisfaction."

Retaining a billing service can reduce your overhead, increase your collections and remove the hassles associated with managing that facet of your practice, but weigh this decision very carefully. Making the initial change can be costly and disruptive. It is not a one size-fits-all proposition. RS

Mr. Laurita is chief operating officer at Retina Associates of Cleveland. Ms. Rasmussen is administrator at Rocky Mountain Retina Consultants, a six-office practice in four western states with the main office in Salt Lake City.

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

Diagnostic Test Challenges

An obvious order and a thorough "interpretation and report" are essential for passing muster in a chart audit.

In the retinal subspecialty, diagnostic testing represents a significant portion of services third-party payers reimburse. The most common testing we see in a retina practice includes scanning computerized ophthalmic digital imaging, otherwise called optical coherence tomography, fundus photography, fluorescein angiography, indocyanine-green angiography and extended ophthalmoscopy.

When we perform chart reviews, documentation associated with diagnostic tests is one of the top areas of exposure. Sometimes indications are not clear, and other times orders are missing; but the most common problem is with documentation of test interpretations.

Interpretations are often missing completely or lacking in content. In this article, I will discuss the documentation standards for diagnostic tests spelled out by Medicare.

Test Orders

Every test that a physician delegates requires an order. The order, based on physician participation, provides the medical necessity for the test. Strict requirements for a physician order exist in the *Code of Federal Regulations*, which states:

> *All diagnostic X-ray tests, diagnostic laboratory tests, and other diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem. Tests not ordered by the physician who is treating the beneficiary are not reasonable and necessary.*[1]

Typically, an order for a test occurs after the physician evaluates the patient, which is most often the case for new patients. For established patients, test orders are often noted on the preceding exam as part of the plan for a return visit. In contrast, some scenarios do exist when the physician has not yet examined the patient, which may also support an order. They are:

- You receive a copy of chart notes from a referring ophthalmologist asking for a consultation, and, after reviewing the referring ophthalmologist's chart notes, you order a diagnostic test to be administered upon the patient's arrival.
- Your technician takes a history and performs a preliminary work-up on a new patient and finds something concerning. The technician brings the information to you, who is scheduled to see this patient soon, and you order an immediate diagnostic test based on the information.

A test personally performed by the physician does not require an order. For example, extended ophthalmoscopy cannot be delegated to ancillary personnel, so an order is not necessary, assuming the indications support the test.

Avoid the use of standing orders. Retina specialists understandably see patients for specific conditions. Establishing a protocol based solely on being a retina specialist does not support an order. Diagnostic test orders should be specific to a patient and generated on a case-by-case basis. Medicare carrier Wisconsin Physician Services stipulates that "standing" or "routine" orders for diagnostic tests are not reimbursable.[2]

Interpretation

The phrase "with interpretation and report" is part of Current Procedural Terminology's (CPT) description for many ophthalmic diagnostic tests. Physicians often ask us, "What exactly does this phrase mean, and what kind of chart note is required?" Because diagnostic tests accompany almost every eye exam retinal specialists perform, this question takes on added urgency because insufficient chart documentation is reason enough to require repayment of any reimbursement as well as brings increased scrutiny from Medicare and other third-party payers.

The Medicare guidelines for interpretation of diagnostic tests are discussed in the *Medicare Claims Processing Manual* (Chapter 13 §100) Interpretation of Diagnostic Tests. The Centers for Medicare and Medicaid Services distinguishes between a review of a test and an "interpretation and report" accordingly:

> *Carriers generally distinguish between an "interpretation and report" of an X-ray or an EKG procedure and a "review" of the procedure. A professional component billing based on a review of the findings of these procedures, without a complete, written report similar to that which would be prepared by a specialist in the field, does not meet the conditions for separate payment of the service. This is because the review is already included in the emergency department evaluation and management (E/M) payment.*[3]

The review of a test is not separately payable because it is part of an E/M service (i.e., an office visit).

> *For example, a notation in the*

(Continued on page 49)

By Richard Mark Kirkner »

Finding More Uses for OCT Angiography

ARVO studies compared OCTA against more invasive imaging, and one even compared OCTA in swept-source vs. spectral-domain platforms.

As retina specialists turn more to optical coherence tomography angiography as a non-invasive alternative for high-resolution imaging of the choroid, the more uses they find for it. Association for Research in Vision and Ophthalmology 2016 devoted an entire track to OCT angiography. Here we report on a few of the innovative ways of using OCTA that ARVO researchers studied.

Of note were two comparative studies involving OCTA: one that evaluated OCTA against fluorescein angiography (FA) in detecting vascularization in diabetic retinopathy; and a second that looked at two different modalities of OCTA—ultra-high speed swept source (SS) and spectral domain (SD)—to visualize choroidal neovascularization (CNV) secondary to age-related macular degeneration.

OCTA vs. FA

In comparing OCTA and FA, researchers from Nagoya University School of Medicine in Japan wanted to get answers about how well OCTA can detect neovascularization and nonperfused areas in eyes with diabetic retinopathy.[1] They performed both OCTA and FA on 34 eyes with diabetic retinopathy.

While they found that both methods yielded the same results in detecting neovascularization—1.9 ±4.0—OCTA actually had an advantage over FA in detecting capillary nonperfused areas: 2.9 ±1.9 vs. 2.2 ±1.8.

"Our findings show that OCT angiography can be used to evaluate the neovascularization and capillary nonperfused areas in eyes with diabetic retinopathy," the investigators concluded. The study investigators had no disclosures.

SS vs. SD OCTA

A team of international investigators determined that SS-OCTA was able to image significantly larger areas of choroidal neovascularization more effectively than SD-OCTA.[2]

They evaluated 14 eyes in 13 patients and found markedly different measurements of CNV depending on what modality of OCTA they used. For 3 mm x 3 mm OCTA, the mean CNV area measured with SS-OCT was 0.949 ±1.168 mm^2 vs. 0.340 ±0.301 mm^2 with SD-OCT. For the 6 mm x 6 mm OCTA, the mean CNV areas were 1.218 ±1.218 mm^2 and 0.604 ±0.592 mm^2 for SS-OCTA and SD-OCTA, respectively.

"It is possible that SS-OCTA is better able to demarcate the full extent of CNV vasculature," the investigators reported. Among the investigators' disclosures were OptoVue and Carl Zeiss Meditec.

OCTAVE Study Results

In the poster session, OCTAVE study investigators reported on their efforts to compare CNV patterns in SD-OCTA, FA and indocyanine green angiography (ICGA) in exudative AMD.[3] They used the following distinct morphologic parameters to characterize neovascular membranes on OCTA images: location; presence of a feeding vessel; presence of an anastomotic arcade; presence of an hypointense perilesional border; and caliber of the neovascular membrane. They also classified these parameters into five different patterns: tree; dead-tree; glomerular; lasso; and fragmented shapes. The primary endpoint was the description of each type of choroidal neovascularization morphology.

In 46 eyes of 43 patients with exudative AMD, OCTA clearly imaged the neovascular complex. The researchers observed types 1, 2 and 4 choroidal neovascularization in 34, 10 and two eyes, respectively, with the glomerular pattern being the most common (38 percent of type 1 CNV and 60 percent of type 2 [$p<0.05$]). In type 4 CNV, the "dead tree" pattern was noted in all eyes ($p<0.05$).

"This study did not identify any differences in OCTA between CNV types as defined by SD-OCT, FA and ICGA," the investigators reported. "Microvascular structures can be delineated accurately and non-invasively, suggesting that this approach provides a safer management of patients with exudative AMD." The study investigators had no disclosures.

By ARVO 2017, we could see even more studies into the utility of OCTA, particularly SS OCTA, in evaluating and characterizing the retinal vasculature in diabetic retinopathy and AMD. RS

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DRCRNET Protocol T 2-Year Data

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Edited by Emmett T. Cunningham, MD, PhD»

APL-2's Role in Blocking the GA Cascade

By inhibiting complement factor C3, Apellis bets it can prevent inflammation in advanced dry AMD.

Flush with an infusion of $47.5 million in financing earlier in the year, Apellis Pharmaceuticals is moving forward to develop agents that inhibit complement factor C3 to prevent geographic atrophy (GA) in dry age-related macular degeneration and a host of other diseases.

Apellis's lead candidates are APL-1 and APL-2, both of which are derivatives of compstatin, a small peptide inhibitor of complement factor C3. The goal is to inhibit local inflammation, tissue damage and dysregulation of the adaptive immune system.

Besides the GA trial, Apellis also has clinical programs to treat paroxysmal nocturnal hemoglobinuria (PNH) as well as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). Both APL-1 and APL-2 are currently being tested in Phase I and Phase II clinical trials, and APL-2 has received Orphan Drug Designation from the Food and Drug Administration to treat PNH.

Cedric Francois, MD, PhD, Apellis founder and chief executive officer, provides insights into APL-1 and APL-2 and the company's Phase II trial of APL-2 for treatment of GA in AMD, known as the FILLY trial. "That has something to do with our affinity for horses since we are based in Kentucky," Dr. Francois says of the trial title.

Long Story Short: FILLY Trial

Formal study title: Study of APL-2 Therapy in Patients with Geographic Atrophy (FILLY).

ClinicalTrials.gov Identifier: NCT02503332.

The mechanism of action in his own words:

APL-1 and APL-2 are both molecules derived from a class of compounds, called compstatin derivatives discovered at the University of Pennsylvania. They bind to complement factor C3 and through steric hindrance, prevent C3 from becoming engaged in the complement cascade. Both of these molecules have been tested in macular degeneration.

The difference between them is that APL-1 is the smallest active peptide, and APL-2 is a derivative of APL-1 that has a longer half life in the eye and will hopefully allow for once-a-month or once-every-other month injections in patients with geographic atrophy.

The role complement factor C3 plays in AMD:

It is still very much a question today why, if it is the case, is uncontrolled complement activation a problem in macular degeneration? Simplistically, this is an issue between two possible pathways. The first is that uncontrolled complement activation damages the retina; an inhibitor to protect the retina acts in a direct cause and effect. In that case, inhibitors of complement factor C5 should work well, because the way in which the complement factor inflicts direct damage on the retina typically goes through C5.

The other way in which the complement factor can be detrimental to the eye is through immunity regulation; so, indirectly, where other adapted immune elements like neutrophils and macrophages are important causes of damage to the retina, complement is really an important regulator of that immune dysfunction. If that is the mechanism by which complement is a problem in the retina, then complement factor C3 is a preferred target to C5.

What is unique about C3 is its central role in how it blocks all the downstream effects of the cascade regardless of the source of activation. In that way, you don't have to

Quotable

"Even through our endpoint is reducing the rate of progression, we are very interested in knowing if we are doing something more profound in these patients that might in the future reduce the need for treatments."

Cedric Francois, MD, PhD

worry about the intricacies of how the complement affects the retina because the goal is to shut the cascade down.

What AMD has in common with other diseases that ALP-2 targets:

What ties these seemingly different programs together is the underlying immunology. Apellis believes that complement as a regulator of immunity is much more important than as a direct insult or destroyer of tissues.

In the underlying immunology at work in IPF, COPD, PNH or macular degeneration, the principal difference between them is the tissue where this immune reaction takes place and the antigens that are involved in this immune process. Inhibiting C3 is a unique way of interfering with the vicious cycle that underlies these conditions.

Status of the current clinical trail in AMD:

With more than 180 of the planned 240 patients currently enrolled, FILLY trial enrollment is almost complete. By the summer of 2017 the trial should provide answers as to whether monthly or every-other-monthly injections of APL-2 in patients with GA can slow disease progression.

The trial design is similar to that of the MAHALO trial of lampalizumab (Genentech), with the object of comparing pathways. But FILLY is not a head-to-head trial; lampalizumab is a factor D inhibitor, and the object of FILLY is to determine how C3 behaves in these patients.

The big question the FILLY aims to answer:

Whether the rate of progression of atrophy in the eyes of patients with dry AMD can be slowed. If it can, it would set up a confirmatory trial.

A point worth adding:

The objective is to explore the immune process that drives the disease. Apellis is much more interested in disease modulation than in symptomatically treating the disease.

"Even through our endpoint is reducing the rate of progression, we are very interested in knowing if we are doing something more profound in these patients that might in the future reduce the need for treatments," Dr. Francois says.

Diagnostic Test Challenges

(Continued from page 44)

medical records saying "fx-tibia" or "EKG-normal" would not suffice as a separately payable interpretation and report of the procedure and should be considered a review of the findings payable through the E/M code. An "interpretation and report" should address the findings, relevant clinical issues, and comparative data (when available)."[3]

Brief notations like "normal, abnormal", or "stable" are construed as a review of the test rather than as an interpretation and report. Define "normal" for each test and use that definition for the occasional normal test results.

Questions a Report Should Answer

Furthermore, noting only the diagnosis as an interpretation is also deficient. Do not overlook a comparative statement regarding the results. Many of the tests retinal specialists order track changes in chronic conditions like age-related macular degeneration and diabetic retinopathy. Consider answering the following questions for a test interpretation:

- What are the results of the test?
- What do the results mean and how do they compare to previous test(s)?
- What are you going to do about the results?

For example, for an OCT, the most common test billed by ophthalmologists within the Medicare program, the "interpretation and report" might read as follows:

- *Subretinal fluid with pigment epithelial detachment OD.*
- *Increased subretinal fluid showing new active wet AMD since last exam 6 wks ago.*
- *Recommend anti-VEGF injection OD.*

Diagnostic tests are a significant part of most practices, so do not underestimate the importance of an obvious order and a thorough "interpretation and report."

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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 when EYLEA was dosed every 4 weeks compared to every 8 weeks.

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

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

2.5 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 when EYLEA was dosed every 4 weeks compared to every 8 weeks.

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.

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

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