Insert to
RETINA TODAY
January/February 2015

Retina In 3-D

A Look Into the Future of Diagnostics, Drugs, and Devices

A Pre Retina Society Summit Meeting

Presented by Wills Eye Hospital

OUR SCIENCE. YOUR ART. THEIR VISION.

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

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

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

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

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

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

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

IMPORTANT PRESCRIBING INFORMATION FOR EYLEA® (aflibercept) INJECTION

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

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

For more information, visit www.EYLEA.com.

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

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

REGENERON

TARGETED SCIENCE

1/2015
LEA-0685

EYLEA® (aflibercept) Injection For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

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

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

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

U.S. License Number 1760
EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

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

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

LEA-0618

Retina in 3-D: Tradition and Innovation Collide

BY JULIA A. HALLER, MD

As important as it is to keep up with publications reporting the latest advances in our field, nothing can supplant the value of face-to-face interactions with colleagues at the cutting edge of new developments.

Wills Eye Hospital was proud to host a premeeting summit prior to the official commencement of the Retina Society 2014 Meeting. The meeting, designed as a collegial "inside scoop" of a gathering targeting the latest in ophthalmologic innovation, was also designed with a nod to the remarkable historic tradition of Philadelphia, sited as it was in the Liberty Ballroom, overlooking Independence Hall and the Liberty Bell, and reflecting the Retina Society's proud tradition of independent thinking, scientific discussion, top level expertise, and intellectual curiosity.

Retina specialists in the 21st century have a continually evolving panoply of drugs, imaging modalities, and surgical instrumentation at our disposal, and the rapid pace of innovation means that options are constantly improving. The premeeting summit was designed to allow participants to delve into a broad menu of cutting edge topics, and to interact with researchers shaping the future scope of retina practice.

Some selected highlights of the summit are featured here. Michael B. Gorin, MD, PhD, discusses the role of genetics in the management of age-related macular degeneration, contributing to the ongoing discussion about the balance of genetic and nongenetic factors in disease progression. Mark Humayun, MD, PhD, and Paulo Falabella, MD, offer an update on the state of retinal prostheses, detailing the limitations and challenges of such devices and giving us a glimpse into their potential. Information on swept-source optical coherence tomography by SriniVas Sadda, MD, sheds light on an imaging modality with tremendous promise to enhance our ability to image and characterize normal and diseased tissues.

Mark C. Van Langeveld, PhD, presenter of this year's Henry and Corinne Bower Lecture, offers an article on the application of 3-D printing in medicine. As futuristic as it may seem, 3-D printers have become markedly less expensive and more efficient in the past decade, such that their applicability and utility have significantly expanded. The specific impact 3-D printing will have on ophthalmology has yet to be determined, but the question is no longer whether but how this technology will play a role in retina—and it behooves us all to understand its nuances.

We are so very lucky to practice in the most exciting and rapidly evolving field in medicine—the one where, as Judah Folkman, MD, iconic clinician-scientist and the father of angiogenesis long ago said to me, the bench is closest to the bedside. We and our colleagues are unrivalled in the value we place on innovation. I hope the articles herein give you some further insights into what will soon become realities in retina, to further direct your practice and your research collaborations. Our patients deserve nothing less. ■

Julia A. Haller, MD, is professor and chair of ophthalmology at Thomas Jefferson University and Ophthalmologist-in-Chief at Wills Eye Hospital in Philadelphia. She is president of the Retina Society. Dr. Haller may be reached at (215) 928-3053 and jhaller@willseye.org.

CONTENTS

Advances in Swept Source Optical Coherence Tomography

Continually improving imaging ability will further improve the ability to diagnose and treat retinal disease.

BY SRINIVAS SADDA, MD

The potential for swept-source optical coherence tomography (SS-OCT) to improve retina specialists' ability to diagnose and treat retina diseases has been talked about for many years. Recent hardware and software advances are moving the technology closer to everyday utility. Although there are still limitations to wide-scale uptake, the greater sensitivity of SS-OCT and the ability to image wider and deeper into ocular structures offer significant advantages over currently available OCT devices (Figures 1 and 2).

CURRENT REASONS FOR NONUSE

Historically, the high cost of SS-OCT technology has prevented their wide-scale adoption. Continued innovation in this field of research, however, may lower cost, thus eliminating a barrier to wider usage. Continued research will also likely contribute to greater durability of SS-OCT machines and the reliability of their output, factors that are important to retina specialists who may use the devices in their offices. Lastly, more studies will need to be conducted to compare findings and measurements from the new SS-OCT instruments with existing SD-OCT devices.

ADVANTAGES OF SS-OCT

SS-OCT offers several advantages over previous OCT modalities, notably faster scanning speed. An overlooked advantage, in my opinion, is that SS-OCT offers greater sensitivity as a function of using tunable dye swept laser light sources and advanced photodetectors. In contrast, spectral-domain OCT (SD-OCT) relies on a broadband light source and a spectrometer to access the frequency-encoded depth information, which unfortunately is associated with a greater loss of signal with depth. Combining improved sensitivity with a longer wavelength for the light source, SS-OCT allows better imaging of deeper structures such as the choroid. Importantly, however, unlike with SD-OCT, SS-OCT allows both the vitreous and choroid to be imaged simultaneously with high signal and tremendous detail.

The high speed and high sensitivity of SS-OCT represent a major advance for the field of en face OCT imaging. En face OCT means viewing OCT image data in the coronal plane (much like how the retina appears by ophthalmoscopy or with typical fundus camera

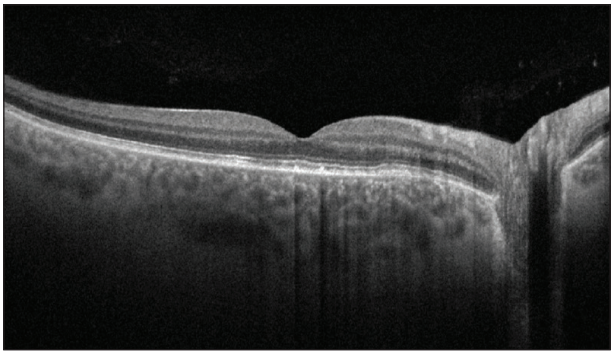

Figure 1. Widefield (12 mm) optical coherence tomography (OCT) B-scan from a prototype swept-source OCT (SS-OCT) device (Carl Zeiss Meditec, not FDA cleared) of a patient with intermediate non-neovascular age-related macular degeneration (AMD). The full-extent of the choroid as well as the lamina cribosa of the optic nerve are well seen.

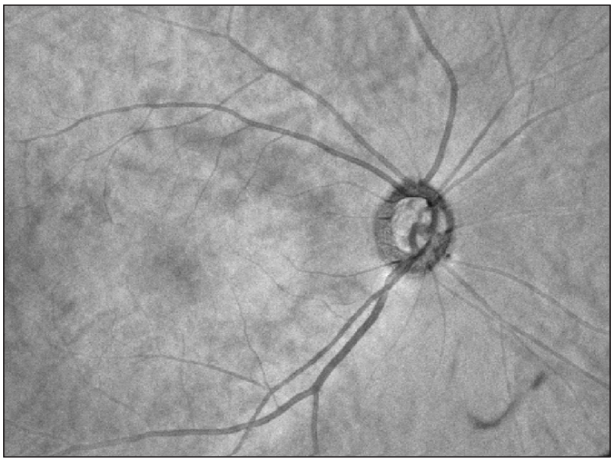

Figure 2. OCT projection image derived from a dense 12 x 9 mm "widefield" SS-OCT volume scan from a prototype SS-OCT device (Carl Zeiss Meditec, not FDA cleared). Note excellent quality of the megapixel OCT projection image, which resembles an infrared reflectance fundus image.

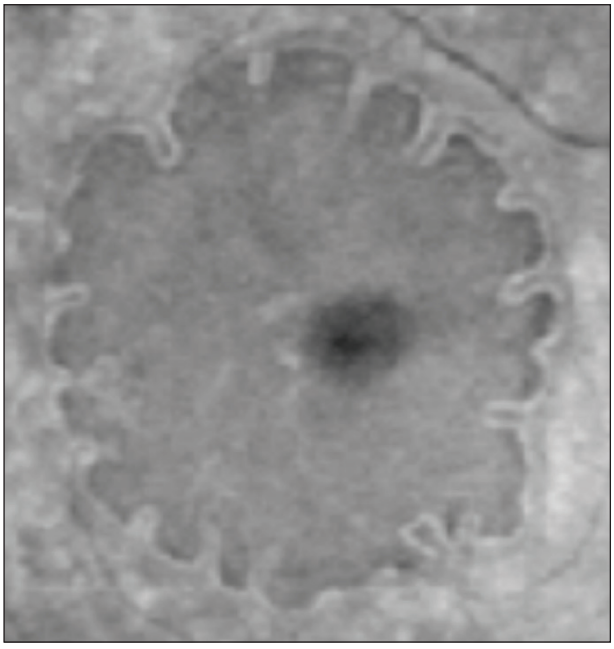

Figure 3. En Face OCT image from a prototype SS-OCT device (Carl Zeiss Meditec, not FDA cleared) at the level of the outer retina in the eye of a patient with geographic atrophy (GA), illustrating the organization of outer retinal tubules in a radial pattern at the margin of the GA lesion.

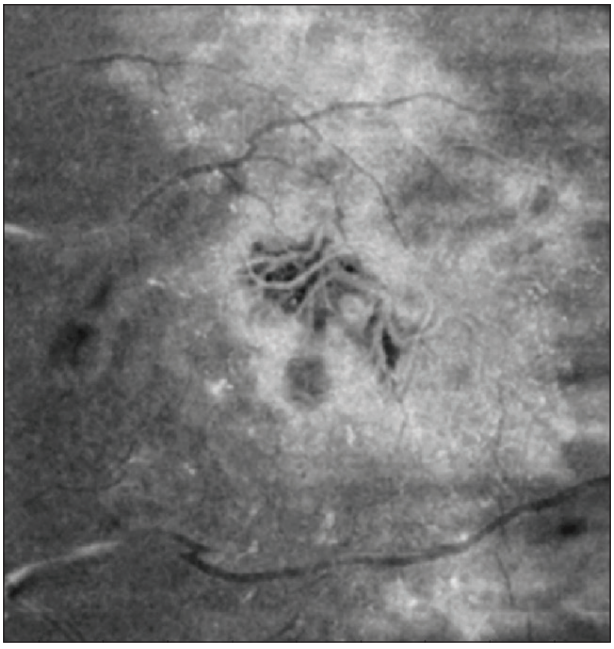

Figure 4. Large vessels within a pigment epithelial detachment of a patient with neovascular AMD revealed by en face SS-OCT imaging with a prototype SS-OCT device (Carl Zeiss Meditec, not FDA cleared).

images), as opposed to the typical axial cross-sectional B-scan imaging. This strategy of imaging has given us new insights into the morphology and pathophysiology of retinal diseases. For example, we now recognize that outer retinal tubules are not randomly organized in areas of atrophy, but rather appear to radiate to the periphery of the lesion (Figure 3).

CASE EXAMPLE

A patient presented to my office with age-related macular degeneration and a pigment epithelial detachment (PED) suspicious for fibrovascular infiltration. En face imaging with SS-OCT at the level of the PED clearly revealed the vascular network consistent with choroidal neovascularization (Figure 4).

En face SS-OCT imaging (perhaps in the future also coupled with OCT angiography), may offer a nice technique to confirm the presence and extent of choroidal neovascularization lesions in patients with suspicious features.

SUMMARY

Clinicians' understanding of retinal disease has progressed at a rapid pace due in large part to improvements in imaging modalities. Our ability to diagnose and treat patients will continue to improve as retina specialists are able to see in greater detail the anatomy of diseased tissue. ■

SriniVas Sadda, MD, is a professor of ophthalmology at the Doheny Eye Institute and University of Southern California in Los Angeles. Dr. Sadda serves as a consultant and receives research support from Carl Zeiss Meditec and Optos. He may be reached at ssadda@doheny.org.

Retinal Prostheses: Advances and Limitations

This technology can help restore independence to patients.

BY MARK HUMAYUN, MD, PHD; AND PAULO FALABELLA, MD

The past decade has seen large-scale innovation in approaches to retinal blindness, especially in the field of retinal prostheses.

ARGUS II

The Argus II Retinal Prosthesis System (Second Sight Medical Products) received European approval (CE Mark) in 2011 and US Food and Drug Administration market approval in 2013 for patients with retinitis pigmentosa (RP), and it remains, to date, the only approved retinal prosthesis worldwide (Figure 1). The systems consists of a 60-channel stimulating microelectrode array that is surgically implanted on the macula, an inductive coil link used to transmit power and data to the internal portion of the implant, an external video processing unit (VPU) powered by a rechargeable battery, and a miniature camera mounted on a pair of glasses. The miniature camera captures video and sends the information to the VPU, which digitizes the signal in real time and creates stimulus pulses based on pixel grayscale values. The stimulus pulses are then delivered to the microelectrode array via the coil.[1] Studies have demonstrated that patients implanted with the device showed positive visual outcomes and toleration of the device.[2-6]

Implantation and use of the device involves interaction between hardware and live tissue, meaning that clinicians must consider the challenges faced by creating an abiotic-biotic interface. This unique and delicate relationship between retinal tissue and the implanted electrode array results in some limitations to this innovative technology.

IRIS-1

The Intelligent Retinal Implant System (IRIS-1, Pixium Vision) is similar to the Argus II in its approach to treating retinal blindness. The device is implanted into the back of eye and connected to a pair of glasses worn by the user. Like the Argus II, the IRIS-1 has an electrode array fixed to the posterior pole. The glasses worn by IRIS-1 users have a fixed miniature camera that transmits images to the electrode array via a receiver located in the patient's pocket. The camera is equipped with an 8x digital zoom and the implant contains approximately 50 electrodes. The IRIS-1 trial, scheduled for completion in early 2015, is expected to provide data on safety and toleration, as well as visual acuity gain at 18 months postimplantion.[7]

Image used with permission from Second Sight Medical Products

Figure 1. An illustration of the Argus II Retinal Prosthesis System showing the coil, cable, and electrode array.

MEASUREMENTS OF TESTING

Static square localization images and visual acuity tests were initially used to measure patients' postimplantation vision. However, researchers found it difficult to employ standard test parameters when evaluating the vision of patients who had been blind for several years. Often, subjects would give an incorrect answer on a particular test, but the incorrect answer was at least an indication of improved visual acuity. Therefore, researches adjusted their expectations and tests to accurately gauge the effectiveness of a device on a patient's vision. Researchers devised algorithms that better evaluated visual improvement in patients implanted with retinal prostheses and applied them on orientation, mobility, and spatial motor tasks. This allowed a greater understanding of the factors underlying performance differences between patients in different tasks.[8-10]

LIMITATIONS AND CHALLENGES

Researchers also ran into limitations when training users how to use the device software, since it has different settings that can be used according to different lighting or contrast conditions. To train the first patient took nearly 18 months; today, training takes approximately 4 to 6 weeks.

Improvements have been made on the device hardware since these products' inceptions, but hardware limitations still pose a problem for some users. Zooming the camera on the IRIS-1, for example, constricts the user's visual field, forcing patients to sacrifice degrees of vision for improved visual acuity. Additionally, reading is difficult for patients with a retinal prosthesis, because some letters are easier to detect than others, and the limited field of vision means that patients can sometimes detect only 1 letter at a time.

Patients sometimes face postsurgical complications due to the interaction of the abiotic-biotic interface, including ocular discomfort surrounding the surgical site, and, less frequently, conjunctival erosion. This could be improved by further lowering the profile of the device and using a scleral graft over it, similar to what is done in glaucoma tube shunt surgeries.[11]

Another challenge is to address the visual field perceived by implanted patients, since the size of the visual field is not a direct function of the size or number of electrode arrays implanted into the eye. Researches have started expanding fields of view by employing digital signal processing, which stimulates the periphery of the electrode array when movement is detected on the periphery of the microcamera. This external image processing—performed by the VPU—compensates for the limited 20° field of vision of the retinal prosthesis, allowing better usability. The same principle has been applied for face detection tasks, enabling the patient to locate human faces in a room with a reduced detection time.[12]

It should be noted that although there are challenges and limitations posed by retinal prostheses, restoration of vision in patients is also a restoration of independence. The ability to again perform routine activities—such as recognizing the presence of people in front of them, identifying doors and windows, and moving around their home — enhances the lifestyle in a cohort of patients who used to be entirely dependent on others.

WHAT DOES THE FUTURE HOLD?

It would appear that with current retinal prostheses, the limit for visual acuity is approximately 20/200. However, some calculations estimate that visual acuity with retinal prostheses could be as high as 20/100 with advanced materials that can conform to the retina and allow higher current density than what is presently possible. The degree of resolution patients can achieve is yet to be determined. ■

Mark S. Humayun, MD, PhD, is the Cornelius J. Pings Chair in Biomedical Sciences, professor of ophthalmology, biomedical engineering, and cell and neurobiology, director of the Institute for Biomedical Therapeutics, and codirector of the USC Eye Institute at the University of Southern California, in Los Angeles. He reports having a financial interest in Second Sight Medical Products. Dr. Humayun may be reached at humayun@med.usc.edu.

Paulo Falabella, MD, is a vitreoretinal surgeon in São Paulo, Brazil, and an associate researcher at the department of ophthalmology, Keck School of Medicine, University of Southern California, in Los Angeles. He reports no conflict of interest related to this article. Dr. Falabella may be reached at p.falabella@usc.edu.

1. Ahuja AK, Yeoh J, Dorn JD, et al. Factors affecting perceptual threshold in Argus II retinal prosthesis subjects. *Trans Vis Sci Technol*. 2013;2(4):1-15.
2. Humayun MS, Dorn JD, da Cruz L, et al. Interim results from the International Trial of Second Sight´s Visual Prosthesis. *Ophthalmology*. 2012;119:779-788.
3. The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. *Br J Ophthalmol*. 2013;97(5):632-636.
4. Rizzo S, Belting C, Cinelli L, et al. The Argus II Retinal Prosthesis: Twelve-month outcomes from a single-study center. *Am J Ophthalmol*. 2014;157(6):1282-1290.
5. Luo YH, Zhong JJ, da Cruz L. The use of Argus II retinal prosthesis by blind subjects to achieve localisation and prehension of objects in 3-dimensional space. *Graefes Arch Clin Exp Ophthalmol*. 2014 Dec 31. [Epub ahead of print]. doi:10.1007/s00417-014-2912-z.
6. Kotecha A, Zhong J, Stewart D, et al. The Argus II prosthesis facilitates reaching and grasping tasks: a case series. *BMC Ophthalmol*. 2014;14(71):1-8.
7. Restoring Vision With the Intelligent Retinal Implant System (IRIS V1) in Patients With Retinal Dystrophy (IRIS-1). ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01864486.
8. Ahuja AK, Dorn JD, Caspi A, et al. Blind subjects implanted with the Argus II retinal prosthesis are able to improve performance in a spatial-motor task. *Br J Ophthalmol*. 2011;95(4):539-543.
9. Humayun MS, Dorn JD, Ahuja AK, et al. Preliminary 6 month results from the Argus II epiretinal prosthesis feasibility study. *Conf Proc IEEE Eng Med Biol Soc*. 2009;4566-4568.
10. Barry MP, Dagnelie G, et al. Use of the Argus II retinal prosthesis to improve visual guidance of fine hand movements. *Invest Ophthalmol Vis Sci*. 2012;53(9):5095-5101.
11. Aslanides IM, Spaeth GL, Schmidt CM, et al. Autologous patch graft in tube shunt surgery. *J Glaucoma*. 1999;8(5):306-309.
12. Stanga P, Sahel J, Mohand-Said S, et al. Face detection using Argus® II retinal prosthesis system. *Invest Ophthalmol Vis Sci*. 2013;54:E-Abstract 1766..

Genetic Testing for Age-Related Macular Degeneration

Genetic testing will have a role in the future of retina practice, but how useful is the information physicians currently curate?

BY MICHAEL B. GORIN, MD, PHD

As the medical community has accepted that age-related macular degeneration (AMD) is a disease influenced by genetics, so too has it uncovered patterns in patients' genetic profiles that suggest some patients are at increased risk for initiation or progression of the disease. However, genetics is not everything, and retina specialists need to remember that AMD is a complex disorder that is also influenced by nongenetic factors.

WHY GENETICS?

There are 2 basic reasons why clinicians and scientists are endeavoring to build genetic or mixed-risk models for AMD. Physicians who are able to identify individuals who will be diagnosed with the disease prior to disease development can take steps to mitigate the disease's onset and/or progression. The second major reason for developing genetic or mixed-risk models is to identify individuals who may exhibit a differential response to therapies, which would allow physicians and patients to selectively and cost-effectively manage the disease.

In the case of early detection, the value of testing is highly dependent on having an intervention that prevents or slows disease. Even if one has the means of identifying patients with differential responses to therapy, physicians must have alternative therapies available to apply differentially based on the risk model. At this time, neither our genetic risk models nor our current treatment options can satisfy their respective requirements. The current interventions for slowing AMD progression are primarily restricted to dietary and lifestyle choices that would be beneficial for the majority of the population regardless of AMD risk. The therapies for treating AMD (currently focused on exudative AMD) may have varying degrees of efficacy based on an individual's genetic risk factors, but at this time there is no rationale for limiting or selecting a particular therapy based on a genetic profile.

Although genetic testing has the potential to shed some light on our understanding of AMD, it also has its limitations. Complex genetic disorders tend to manifest a spectrum of clinical features and it is unlikely that one can simply attribute specific features, such as type of drusen or polypoidal choroidopathy, to a specific set of genetic variants. One can perhaps show differing contributions of multiple genes to some AMD features and this may help researchers better understand their pathogenesis. In some cases, shared associations of genetic variants (such as those that are associated with AMD and those with polypoidal choroidopathy) may indicate shared pathways of pathogenesis.

DEVELOPING A RISK MODEL FOR MACULAR DEGENERATION

Retina specialists must rely on evidence-based methods for using genetic information to inform their patient counseling and treatment decisions. Molecular genetic testing is not a substitute for taking an appropriate family history and such information should be used in an integrated manner.

Given the current sensitivity and specificity of AMD risk models based solely on genetic factors, using such testing for the general population will result in an excess of false positive tests. One can reduce the percentage of false positives by limiting the population to be tested to those who have an already elevated risk of disease due to family history, early clinical findings, and known risk factors (such as smoking). The most effective current risk models incorporate genetics as well as these other components, with more than half of the risk determined by the presence of clinical findings that are associated with early AMD.

There is considerable interest in finding potential biomarkers in the blood that may indicate altered inflammatory, lipid, metabolic, or immune states that contribute to AMD. There is also great interest in identifying clinical markers of early retinal dysfunction or structural changes. Combining molecular genetic profiles with clinical markers may create risk models that are sufficiently sensitive and specific to serve as part of clinical care.

LIMITATIONS OF GENETIC TESTING

The presence of AMD-associated variants in noncoding regions presents a challenge for our understanding

of molecular genetics. Some of these variants may affect levels of transcription of a distant gene, alter the pattern of alternative splicing, or even affect the transcription of embedded genetic elements that are not translated into proteins but serve a regulatory role in the cell. Even after complete genomic sequencing, any determination of disease likelihood for a patient is limited because the possible variants in every critical region of DNA cannot be identified. Patients should be advised during genetic counseling sessions that a negative test result—such as one that does not identify a genetic variant—does not mean that they have no risk for a particular disease; it simply means that no risk was identified. This is especially true for individuals who have a positive family history for AMD and are concerned about their own risk of developing the disease. The current genetic tests do not include rare variants that may influence heritability within an AMD family and the risk profile based on common variants may be misleading.

It is important to note that the phenotypic expression of genetic variations first learned in Mendelian genetics become more complex and varied as scientists understand more about the human genome. Mutations can result in a number of phenotypes. For example, patients who have the ABCA4 mutation have phenotypic expressions ranging from Stargardt disease, to AMD, to cone dystrophy. Thus, the presence of a certain phenotype is not necessarily associated with specific genes or variants. These are some of the uncertainties that one has to accept when dealing in genetic profiling.

There have been no reliable data establishing a clear-cut relationship between genetic profiles and the severity or rate of progression of AMD. Most of the associations of genetic variants with AMD have concerned different stages of AMD (early, intermediate, or late/advanced) compared with controls, but not with the rates of progression of the condition or of specific phenotypic features such as drusen. Only the RetnaGene test (Nicox Inc. and Sequenom Laboratories), which includes genetic and nongenetic factors, has been validated with longitudinal data from the AREDS cohort and offers some prediction of disease progression.[1]

SHOULD WE DO GENETIC TESTING FOR AMD?

Our understanding of the complex relationship between genetic profiles and phenotypic expression continues to evolve as a dynamic model, and genetic tests currently available are not yet sophisticated enough to reliably guide treatment decisions. Current tests are not effective in diagnosis or management, and therefore should not be used. Physicians trying to reinforce medical recommendations by pointing to an elevated genetic risk for a particular condition could be employing a form of coercion, especially considering the considerable uncertainty that the patient will actually develop disease in question. Because all patients would benefit from current recommendations (ie, healthy diet, smoking cessation, etc.), and considering that those recommendation possess little or no risk, physicians should not need to resort to genetic profiling. ■

Michael B. Gorin, MD, PhD, is the Harold and Pauline Price Professor of Ophthalmology and chief of the retinal disorders and ophthalmic genetic division at the Jules Stein Eye Institute at the University of California, Los Angeles.
He receives funding from the Harold and Pauline Price Foundation, Research to Prevent Blindness, and the Stein Eye Institute. He is a coinventor of a patent held by the University of Pittsburgh for the 10q26 AMD susceptibility locus that has been licensed to Sequenom. *Dr. Gorin may be reached at gorin@jsei.ucla.edu.*

1. Hageman GS, Gehrs K, Lejnine S, et al. Clinical validation of a genetic model to estimate the risk of developing choroidal neovascular age-related macular degeneration. *Hum Genomics*. 2011;5(5):420-40.

Medical Applications of 3-D Printing

As 3-D printing becomes more commonplace, the possibilities for its applications in medicine are expected to grow.

BY MARK C. VAN LANGEVELD, PHD

Although they seem like plot devices from science fiction films, the prevalence and practical use of 3-D printers are increasing. From the assembly line to the artist's studio, 3-D printing has given users the ability to create objects with different colors, densities, and mechanics. 3-D printers, for example, allow a mechanic restoring a vintage motorcycle to create a part of an engine that has not been manufactured for several decades.

Emerging technologies have reduced the costs associated with 3-D printing, have introduced new materials to printers, and have allowed the printers to craft complex and sophisticated products; thus, technological (both hardware and software) innovations have widened the potential for more common applications of 3-D printing.

The advent of 3-D printing is the inevitable result of the tradition of manufacturing, beginning with the printing press, moving toward the assembly line, and ending (for now) with 3-D printers that employ mechanisms similar to large-scale ink printers. If we consider 3-D printing as part of, rather than a departure from, this tradition, then we can begin to understand the possible applications of 3-D printing.

THE PROCESS

Three-dimensional printing is an additive process. A 3-D printer lays ultra-refined material between thin layers of adhesive, creating a 3-D object in small increments (as small as 1/400 of 1 inch) in millions of layers. After the printer is finished adding material, extra material (either dust or whatever skeleton is used during the printing process) is removed and, depending on the material used in the printing process, the mold is hardened with a strong coating material.

The algorithms assigned to the printer for particular objects to be printed have grown in complexity, allowing for greater sophistication in both objects printed and their structural integrity. Algorithms employing honeycomb architecture, for example, increase the strength of a printed object and decrease its weight. Other algorithms introduced materials such as glass, ceramics, and biologic tissue as mediums of creation.

3-D BIOPRINTING

Three-dimensional printing has a wide variety of uses in the medical field, from creating more comfortable prosthetics to replicating biologic tissue. Surgeons at the Children's Hospital of Philadelphia, for example, have created 3-D–printed replicas of pediatric hearts using a soft polymer material. These replicas, examined by surgeons prior to surgery, allow surgeons to preview the specific heart of a particular patient, either by breaking the replica into pieces to peer inside the organ or to perform a dress-rehearsal surgery. The 3-D printed replicas are created from data taken from the actual model by 3-D imaging techniques, such as data from magnetic resonance imaging scans.

Three-dimensional printing can create miniature objects that would otherwise be very difficult to manufacture. Cochlear implants, for example, have been created via 3-D printing. Surgeons at the University of Utah are using 3-D printers to create portions of jawbones that need repair using a bone-like polymer process.

When we consider that 3-D printing can be used to create very small objects, we can imagine that the opportunities in the ophthalmic world are many. For example, with 3-D bioprinting, the designing and printing of corneas are being tested. As the materials progress in 3-D printing, there are many other replacement ophthalmic parts that could be custom printed, including lenses. As we invent more control for matching nerves, we will be able to print biomaterial for the sclera, choroid, and even the retina.

SUMMARY

3-D printing is still in its infancy. We are far away from the days of in-home 3-D printers preparing Thanksgiving dinner. However, innovations in this technology in the past decade give those in the medical community a new tool to use in their field. As technology improves and costs decrease, expect to see 3-D printing incorporated into medical practice. ■

Mark C. van Langeveld, PhD, is assistant professor in the School Of Computing, and associate professor in Entertainment Arts Engineering at the University of Utah in Salt Lake City. Dr. Van Langeveld reports no conflict of interest related to this article. He may be reached at vanlange@cs.utah.edu.

RETINA TODAY