An Update on the Intravitreal Injection Procedure

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Genetic Testing for Age-Related Macular Degeneration

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10 ARVO Abstracts Worth a Second Look

PAGE 34
A different perspective can have the power to change your approach

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

**Dosage and Administration**
FOR OPHTHALMIC INTRAVITREAL INJECTION.
The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

**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.

**Adverse Reactions**
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 (8%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous
The pathophysiology
— An inflammatory cascade plays a key role

The therapeutic targets
— Suppress multiple inflammatory cytokines

The clinical results
— Achieve clinically significant 3-line gains in BCVA

The #1 steroid in U.S. market share for DME

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
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 23% of OZURDEX® (dexamethasone intravitreal implant) patients versus 4% of sham patients. 42% of the patients who received OZURDEX® (dexamethasone intravitreal implant) 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® (dexamethasone intravitreal implant) 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.

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

*Best-corrected visual acuity
Based on U.S. market share of DME patients treated with intravitreal steroids: December 2014.

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

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 Pericocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or pericocular 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.

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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® may not reflect the rates observed in practice.

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

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=324 (%)</th>
<th>Sham N=328 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td></td>
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<tr>
<td>Cataract</td>
<td>166/243 (68%)</td>
<td>49/230 (21%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>73 (23%)</td>
<td>44 (13%)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>28 (9%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>19 (6%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>16 (5%)</td>
<td>6 (2%)</td>
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<tr>
<td>Conjunctival edema</td>
<td>15 (5%)</td>
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<td>Dry eye</td>
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Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

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<td>≥30 mm Hg IOP at any visit</td>
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* 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; 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.

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

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**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, gastrochisis 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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Consequences Of Surviving The Black Death

Current estimates indicate that more than 50 percent of your age-related macular degeneration (AMD) risk is genetic. Why is AMD prevalence highest among fair-skinned individuals of European descent?

Dr. Robert Avery, a friend and colleague, has proposed a captivating theory. During the Middle Ages and peaking in the mid-1300s, the plague, or Black Death, ravaged continental Europe and reduced world population from 450 to 350 million. During this time, infection with Yersinia pestis had a mortality rate of about 50 percent. Intriguingly, complement polymorphisms, specifically the Y402H allotype of Complement Factor H, may enhance an individual’s ability to identify and eradicate Yersinia pestis. Such polymorphisms may have conferred a survival benefit to those facing the plague, thereby creating a strong selection pressure in affected populations. As life expectancy subsequently increased, collateral effects of these enriched genetic alterations have become apparent in increasing AMD risk.

Similar theoretical genetic links between other medical maladies and infectious diseases, including sickle cell disease and malaria, are fascinating and may shed light on human circumstances over thousands of years.

As our understanding of AMD genetics has advanced, so has our ability to treat associated neovascularization, raising new questions. For example, does VEGF blockade affect the development or progression of macular atrophy?

In this issue, we explore the role of genetic testing and the relationship between anti-VEGF treatment and macular atrophy, pertinent issues for our management of AMD patients and their families, whose younger generations are often concerned about their personal AMD risk.

My mother has intermediate dry AMD and my grandmother may have been blind from AMD. While I have not undergone formal genetic testing, I likely harbor some of the AMD genetic polymorphisms discussed in these pages. I wonder if my immune system could withstand a bout with Yersinia, and I wonder when data will indicate is the time for me to systematically offer genetic testing to my patients and their families.

REFERENCE:
1. Avery RL. The plague and macular degeneration. Ophthalmology. 2010;117: 2442
Retina Specialist focuses on the latest advances in the diagnosis, medical management and surgical treatment of diseases of the retina, along with practical, real-world advice from leading clinicians and other experts on managing the successful retina practice.

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*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

† For patients with moderate to advanced age-related macular degeneration.

Only PreserVision® AREDS 2 Formula contains the exact ingredient dosages recommended by the National Eye Institute† based on the evidence from the AREDS2 study."
IN BRIEF

- **Ampio Pharmaceuticals Inc.** announced positive results of the OptimEyes trial of its oral Optina drug for diabetic macular edema. In a subgroup of patients based on body-mass index, 53 percent of those who were unresponsive to existing intravitreal injections showed a 6.2 letter improvement in visual acuity over three months; the remaining 47 percent, who were unable or unwilling to have intravitreal injections, showed a 3.1 letter improvement over the same period.

- **Ophthotech Corp.** has completed patient recruitment for its first Phase III trial of its Fovista anti-PDGF drug in combination with ranibizumab (Lucentis) in wet age-related macular degeneration. The company expects to complete patient recruitment in the second Phase III trial of combination Fovista-Lucentis by the end of the third quarter this year. Ophthotech expects topline data from both trials to be available in 2016. Meanwhile, a third Phase III trial investigating Fovista in combination with aflibercept (Eylea) or bevacizumab (Avastin) is currently recruiting patients.

- **Spark Therapeutics Inc.** acquired exclusive rights to license Clearside Biomedical Inc.’s microinjector technology to deliver gene therapies to the back of the eye. Under the agreement, the companies will explore the feasibility of using Clearside’s microinjector technology to deliver viral vectors to the choroid and the retina through the suprachoroidal space.

- **ThromboGenics NV** is evaluating ocirplasmin (Jetrea) as a potential treatment for retinal vein occlusion (RVO). The new research will build on earlier ThromboGenics Phase IIa data pointing out the potential of ocirplasmin for the treatment of peripheral arterial occlusions, the company says. With this new vitreoretinal project, ThromboGenics aims to demonstrate the potential of using locally delivered ocirplasmin for lysing the blood clots responsible for RVO in diabetic macular edema.

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**Proposed FDA Rule Could Limit Supplies Of Bevacizumab**

The Food and Drug Administration (FDA) is considering new guidelines that may severely limit the supply of bevacizumab (Avastin, Genentech) in retina specialists’ offices, so the American Society of Retina Specialists (ASRS) has generated more than 300 comments stating that bevacizumab for ocular use should be exempted from the new regulations.

“The proposed FDA guidance on repackaging of biologics is very strict and will greatly curtail use of Avastin in the clinic,” says Geoffrey Emerson, MD, PhD, chair of the ASRS Federal Affairs Committee. “The guidance as written makes it very difficult to order, receive and administer Avastin in the time allowed by the FDA.” That could force retina specialists to use the more costly Lucentis (ranibizumab, Genentech) or Eylea (aflibercept, Regeneron) instead.

The FDA’s proposed rules would restrict beyond-use dates (BUDs) for traditional compounders and outsourcing facilities. Compounders may continue to repackage bevacizumab for ophthalmic use, but the proposed BUDs would make it “extremely difficult” for ophthalmologists to order and store bevacizumab for office use, states an ASRS analysis of the rules. ASRS is urging the FDA to set aside the proposed BUDs and focus instead on the science.

For traditional compounders, the proposed BUDs are up to four hours or whatever the labeling states the allotted time within which the opened product should be used, whichever is shorter; or up to 24 hours if microbial challenge studies have demonstrated that microbial growth of the repackaged formulation will not reach a harmful level within the BUD period. Traditional compounders will still need a patient-specific prescription to dispense bevacizumab.

For outsourcing facilities, BUDs would be the same with one additional mandate: five days or less or the expiration date of the product being repackaged, whichever is shorter—provided the outsourcing facility performs compatibility studies on its repackaging system to verify product integrity.

The challenge with bevacizumab relates to its off-label use for age-related macular degeneration and diabetic retinopathy. Ranibizumab and aflibercept come in glass vials with an expiration date two years after their manufacture; bevacizumab comes in 100- or 400-mg vials, which are used for intravenous infusion to treat colon cancer, Dr. Emerson explains. For use in the eye, compounders and outsourcing facilities must repackage the drug from the manufacturer’s glass vial into smaller vials or plastic syringes.

“According to the proposed FDA guidance, the BUD for repackaged
Avastin will be a maximum of one day for a traditional compounding pharmacy and five days for an outsourcing facility,” Dr. Emerson says. “The proposed BUDs are very short compared to the standard practice that has been in place for the past 10 years, with BUDs of typically three to six months.”

The proposed BUDs would make it impossible for retina specialists to perform 14-day sterility testing on the repackaged bevacizumab. “Many retina specialists insist that sterility testing is required for patient safety,” Dr. Emerson says. “Second, the logistics of ordering, receiving and administering Avastin will be extremely rushed and complex given the proposed one- and five-day BUDs, and it may be impossible to have repackaged Avastin available for use on Monday or Tuesday depending on whether a compounding pharmacy or outsourcing facility repackaged and shipped during the weekend.”

The comment period for the proposed rule change closed in May, but the process of issuing the final rule could take months.

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**21st Century Cures Would Restore NIH, NEI Funding**

Legislation that would restore funding to the National Institutes of Health and the National Eye Institute is moving through Congress with uncharacteristic bipartisan support.

The House Energy and Commerce Committee in May approved the 21st Century Cures Act by a 51-0 vote. The act would increase overall NIH funding $1.5 billion a year over each of the next three fiscal years and provide an additional $10 billion over the next five years for the NIH Innovation Fund.

“A rising tide lifts all boats, so increased NIH funding ideally would mean additional funding for the institutes and centers,” James Jorkasky, executive director of the National Alliance for Eye and Vision Research. The Innovation Fund would target emerging scientists, high-risk, high-reward research and big-ticket infectious disease research, Mr. Jorkasky says. “There’s opportunity there for vision researchers,” he says.

Several hurdles remain before the funding appears. The full House has to vote on the bill, and the Senate, where the Health Education and Labor and Pensions Committee is coordinating legislation with the House committee, must also pass it. Then there’s the matter of actually getting the appropriations from Congress; 21st Century Cures is merely an authorization, not an appropriation.

Robert Eugene Anderson, MD, PhD, director of research at Dean McGee Eye Institute at the University of Oklahoma and a longtime advocate for vision research with the Association for Research in Vision and Ophthalmology, says the potential for more medical research funding would reverse a devastating trend over the past decade.

“As far as the NEI is concerned, we’ve gone from more than 1,200 to a little more than 1,000 R01 research grants today; that’s about a 15 percent cut,” Dr. Anderson says. R01 is an original NIH grant category that allows the investigator to define the focus of the research.
The Controversy of Band #2

*What should we call the second of four outer retinal hyperreflective bands on OCT imaging?*

**Band #2** has been given various names in the past. In the early years of optical coherence tomography (OCT) imaging, the band was mislabeled and confused with adjacent hyperreflective bands, or it wasn’t named at all, or was just called it “the red line” because of its high reflectivity in the false color display mode.

Soon the correlation to anatomical structures was narrowed down to the inner segment/outer segment (IS/OS) junction or ellipsoid zone (EZ). Throughout the literature, depending on research group, both terms were used and associated with band #2. Even within the same paper, band #2 was correlated to the EZ in one figure and named the IS/OS in another.

Despite the confusion of what to call band #2 and the anatomical structure correlated with it, consensus at least exists on the appearance of this band: It reflects photoreceptor integrity and health, and its absence is a poor prognostic sign.

Here, we explore the anatomy of the region and discuss two of the terms that have been used to describe it.

**Anatomy of Band #2 Region**

The inner segment of each photoreceptor is comprised of an IS myoid and an IS ellipsoid (ISel). The ISel is the distal-most portion of the IS and adjacent to the IS/OS junction. About 75 percent of the content of the ISel is tightly packed with mitochondria. In a healthy retina, ISel mitochondria are long, thin and bundled parallel like uncooked spaghetti.

The IS and OS is connected by a cilium, measuring approximately 0.25 µm by 1 µm, which is comprised of microtubules. A narrow gap (50-200 nm), can be seen on electron microscopic (EM) imaging and separates the IS from the OS. It’s not quite clear if this gap is real or an artifact. This passage, which includes the connecting cilium, is called the IS/OS junction.

**Nomenclature: Pro-Ellipsoid Zone**

The term “Ellipsoid Zone” arises from the reflectivity source of OCT band #2 correlating with the ISel. When authors compared OCT band #2 with histologic images, the apparent source of the signal appeared to correlate with the ISel, presumably arising from the ISel mitochondria. The ovoid mitochondria with multiple internal membranes (cristae) were thought to contribute to a high refractive index in this region and optically serve as microlenses.

The work of physicists, through the use of adaptive optics (AO) ultra-high resolution OCT (UHR-OCT) imaging, supported these conclusions. UHR-OCT with pancerrection seemed to elongate band #2, resembling the true axial morphology of cones, and correlated to the ISel. Because photoreceptors have high metabolic needs and require an excess of large mitochondria, their orientation in the ISel could suggest an arrangement that would yield optical benefit beyond their role in energy production.

Genetic studies in which the age-related maculopathy susceptibility 2 (ARMS2) gene plays a role in age-related macular degeneration (AMD) have implied the importance of mitochondria and band #2, possibly through a mitochondria-related pathway. ARMS2 encodes for a mitochondrial protein found with ISel. A reported decreased intensity of the band #2 signal in AMD patients further supported this theory, but this may reflect a more general finding of photoreceptor dysfunction.

Moreover, electron micrographic images of photoreceptor degeneration, as in outer retinal tubulation (ORT), revealed morphologic changes in the ISel mitochondria. The mitochondria in these photoreceptors lost their well-structured arrangement and were randomly scattered, shortened and displaced toward the nucleus. In a 1:1 cor-
relation between OCT and histology of a patient with ORT, a hyper-reflective band was seen on OCT and the reflectivity source was correlated with histology and EM images. The images revealed short, randomly scattered mitochondria on both sides of the external limiting membrane and an absent OS. In this case, the hyper-reflective band on OCT could not represent the IS/OS junction, because OS were not present.13 However, it remains to be determined whether the reflective bands associated with ORT can even be correlated with reflective bands arising from normal retina since the anatomy is so deranged.

A 2011 paper correlated band #2 to the EZ based on distance measurements to adjacent hyper-reflective bands and thickness measurements of band #2 itself using Spectralis SD-OCT (Heidelberg Engineering).4 These authors correlated OCT findings to a photoreceptor model, which they created based on histologic measurements they obtained in a broad literature review. They found the thickness of band #2 to be similar to the anatomical measurements of the ISel portion.

In an attempt to reach a consensus on the terminology for retinal layers and the bands that appear on SD-OCT imaging, a panel of retinal specialists proposed a nomenclature for the posterior segment, choosing to call band #2 the EZ.14 However,
ISel serves as a waveguide, and its contribution to the Stiles-Crawford effect is widely accepted. This is not surprising when having a closer look at the arrangement of the mitochondria in the ISel (long, thin and bundled), which resembles fiber optics and increases in number with eccentricity. The OCT back-reflection from the IS/OS region seems to arise from the abrupt change in optical index of refraction at the IS/OS junction, and the ISel mitochondria (lipid rich) are thought to contribute to the high refractive index of the inner segment.

**Which Sides to Take?**

So, which nomenclature is correct? Does band #2 correspond to the high reflectivity of the ISel mitochondria or is it the contribution to a refractive index change between IS and OS that’s responsible for generating band #2 at the level of the IS/OS junction? Both waveguiding and scattering contribute to this photoreceptor hyper-reflective band.

There’s no correct answer at this time and band #2 is referred to interchangeably as the IS/OS band or the EZ band. Regardless of your terminology, it’s important to acknowledge the research and theories from both sides and appreciate the significance of retinal anatomy and the OCT band toward understanding the principles of OCT imaging and outer photoreceptor pathology.

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A Case of Blurry Vision and Photopsias

Could a history of uveitis have a role in acute, unilateral worsening vision over three days?

By Benjamin Y. Xu, MD, PhD and Meena George, MD, PhD

An 18-year-old Caucasian man presented to the Retina Service at the USC Eye Institute complaining of photopsias and blurry vision in his left eye. The patient first noticed intermittent flashes three days before the visit, followed by progressive worsening of his vision. He denied pain, redness, photophobia, floaters, curtains, trauma, recent illness, headache, tinnitus, fever, chills, cough, rash and any prior episodes.

History

The patient recalled an episode of anterior uveitis in both eyes several years before. A work-up at the time was negative. He was taking difluprednate b.i.d. OU as prophylaxis and denied recurrence of uveitis symptoms since the initial episode. His ocular, medical and surgical histories were otherwise negative. He had no allergies and was not taking any medications aside from the difluprednate. The patient was a student with upcoming examinations.

Examination

Best-corrected visual acuity (BCVA) was 20/20 OD and 20/200 OS. Intraocular pressure was 16 mm Hg OD and 14 mm Hg OS. Pupils were round and reactive without a relative afferent pupillary defect. Color plates were 10/10 OD and 7/10 OS. Slit lamp examination showed more posterior synechiae in the left eye, but no cell, flare or keratic precipitates. The dilated fundus exam showed scattered, faint, white, placoid lesions of less than one disc diameter along the superior arcade and temporal macula (Figure IA). These lesions were bilateral, but more prominent and numerous OS, involving the central macula and temporal periphery (Figure 1B).

Diagnosis, Workup, Treatment

Given the characteristic white placoid lesions in both eyes, the differential diagnosis included primary inflammatory choriocapillaropathies, also referred to as the “white dot syndromes,” such as acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and multiple evanescent white dot syndrome (MEWDS). We also considered autoimmune etiologies such as Vogt-Koyanagi-Harada (VKH) disease, systemic lupus erythematosus (SLE) and sarcoidosis, and infectious etiologies such as tuberculosis, syphilis and Lyme disease. Optical coherence tomography (OCT) OS showed dome-shaped elevations of the ellipsoid zone (EZ) band with pockets of hyper-reflective material and subretinal fluid OS (Figure 2A, page 16). OCT OD was unremarkable.

Fluorescein angiogram (FA) OS showed early hypofluorescence (Figure 1D) with late hyperfluorescence at the sites of the placoid lesions. Late frames OD showed hyperfluorescence in more regions of the temporal macula and periphery than the fundus exam (Figure 1C). Fundus autofluorescence (FAF) was largely unremarkable. Indocyanine green angiography (ICGA) showed numerous prominent foci of hypofluorescence in the temporal macula OD (Figure 1E). This finding was more prominent OS with large confluent patches of hypofluorescence covering the macula (Figure 1F). In both eyes, the number of hypofluorescent lesions...
was much greater than the number of lesions seen on the fundus exam and FA.

Our initial workup, which included chest x-ray and tuberculosis (PPD), syphilis, antinuclear antibody and Lyme/Bartonella/herpes simplex/ cytomegalovirus titers, came back negative two days later.

We started the patient on prednisone 40 mg PO daily. One week later, best corrected visual acuity was 20/60 OS and the photopsias had resolved. We saw the patient multiple times over the next few weeks. His vision continued to improve, reaching 20/30 after one month of therapy, at which point we slowly tapered the prednisone.

Also, the subretinal fluid OS seen on OCT had improved, although mild granularity of the EZ band at the site of the placoid lesions was still present (Figure 2B). These OCT changes, along with the placoid lesions seen on fundus exam, resolved by month three (Figure 2C). By month six, BCVA OS was 20/20.

Discussion

Primary inflammatory choriocapillaropathy or choriocapillarisitis are terms that describe most of the diseases classified as “white dot syndromes;” they include APMPPE, MEWDS, multifocal choroiditis and serpiginous choroiditis. The disease mechanism that unifies these conditions is reduced perfusion within the choriocapillaris, presumably from localized inflammation, although the underlying etiology is not well understood. ICGA is an excellent technique to investigate suspected cases of choriocapillarisitis; it can reveal areas of hypo- or non-perfusion within the choriocapillaris that lead to retinal ischemia and outer retinal pathology. ICGA also corresponds better to patients’ performance on functional tests such as visual fields than a fundus exam or FA.

APMPPE typically presents in young adults with bilateral vision loss and may be preceded by a viral illness. Presenting symptoms may include photopsias, decreased vision, paracentral scotoma and metamorphopsia. Interestingly, this young patient only had unilateral symptoms despite the presence of bilateral pathology, and he did not recall any prior viral illness. Our patient displayed the classic fundus lesions that characterize APMPPE—scattered, flat, multifocal, creamy white or yellow lesions at the level of the retinal pigment epithelium (RPE). Lesions are typically located in the macula but may also involve the peripheral retina.

On FA, active lesions demonstrate characteristic early hypofluorescence and late hyperfluorescence. Early hypofluorescence is thought to result from blockage secondary to inflammation and edema of the RPE. Late hyperfluorescence results from staining of the damaged RPE and leakage from the underlying choriocapillaris. Chronic lesions show hyperfluorescence corresponding to window defects from RPE atrophy.

Our patient’s FA was consistent with the findings described here, supporting a diagnosis of APMPPE. FAF may show hypoautofluorescence of lesions in the acute phase that persists even with lesion resolution. Hyperautofluorescence may also occur late due to deposition of lipofuscin or altered metabolism of affected RPE. This particular case of APMPPE did not demonstrate such changes on FAF.

Recent analyses of APMPPE lesions using spectral-domain OCT have demonstrated various stages of retinal changes. At onset, placoid lesions appear as prominent, dome-shaped elevations of the EZ band, with pockets of hyper-reflectivity and subretinal fluid; imaging after one-month of prednisone treatment (B) shows mild granularity of the EZ band and improvement; and after three months and complete tapering of prednisone (C), OCT shows resolution of earlier pathology.

Figure 2. Optical coherence tomography (OCT) of the left eye: initial presentation (A) shows dome-shaped elevations of ellipsoid zone (EZ) band with pockets of hyper-reflectivity and subretinal fluid; imaging after one-month of prednisone treatment (B) shows mild granularity of the EZ band and improvement; and after three months and complete tapering of prednisone (C), OCT shows resolution of earlier pathology.
the RPE sustains minimal residual irregularity. Our patient’s OCT OS appeared to follow this course, with improvement of vision corresponding to decreased subretinal fluid and restoration of the EZ band.

Over a course of approximately two to four weeks, active APMPPE lesions seen on fundus exam resolve spontaneously, often with motting of the RPE but without atrophy of the choroid. Visual prognosis is usually excellent, with most patients achieving a visual acuity of 20/40 or better. However, prognosis is less favorable when the fovea is involved.

Because of our patient’s functional requirements, foveal involvement OS and extent of vision loss OS, we decided to treat early with oral prednisone. Uncommon cases of severe vision loss from persistent RPE alterations in the fovea have been reported. Choroidal neovascularization can also complicate APMPPE. Recurrences of APMPPE are rare.

Finally, several reports have linked APMPPE to central nervous system vasculitis, with manifestations ranging from headaches to venous sinus thrombosis. The combination of APMPPE with neurologic manifestations occurs more frequently in men and very rarely can have dire consequences, including death. Thus, a thorough review of systems is critical for any patient presenting with a possible diagnosis of APMPPE. Treatment recommendations in such cases include IV corticosteroids followed by a slow oral taper in combination with an immunosuppressant.

**Conclusion**

This case demonstrates the multiple classic exam and imaging findings associated with APMPPE. It also highlights the utility of ICGA in the diagnosis of APMPPE and other forms of choriocapillaritis. It underscores the importance of performing a full work-up for autoimmune and infectious etiologies before arriving at the diagnosis of APMPPE. Steroid treatment may offer a more favorable prognosis when the fovea is involved.

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**USC Eye Institute**

Dr. Olmos de Koo is an assistant professor of ophthalmology at University of Southern California Eye Institute and the director of the vitreoretinal fellowship at the Keck School of Medicine of USC in Los Angeles.

Dr. Xu is an ophthalmology resident at USC Eye Institute/ Los Angeles County + USC program. Dr. George is a vitreoretinal surgical fellow at USC Eye Institute.

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**THE RICK BAY FOUNDATION**

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Anti-VEGF therapies have now been available for many years, and we are seeing patients that first initiated therapy five years ago or longer. We are starting to see that these patients may go on to lose vision over time. And we are observing that many of them with wet age-related macular degeneration (AMD) go on to develop atrophy.

Recent studies have raised various questions about causes of atrophy in treated wet AMD. They include: Is it the natural progression of underlying dry AMD that drives the atrophy? Or is macular atrophy associated with the choroidal neovascularization (CNV) lesion? Or is macular atrophy associated with anti-VEGF therapy independent of CNV? And lastly, should what we know so far affect my management of patients?

Unfortunately, the studies and data that we have to date are really not designed to answer these crucial questions. In addition, as clinicians and researchers we struggle with the very definitions and identification of atrophy in the setting of wet AMD. It is important to remember that before anti-VEGF therapy, these patients were going on to develop large fibrotic disciform scars, and atrophy in this setting was not a major consideration. Certainly, no consensus exists with regards to the best diagnostic tools and methodology to detect and assess the progression of atrophy in this setting.

Despite these significant limitations, exploring what we know and don’t know at this point and considering how we should use this information in counseling our patients is a worthwhile exercise.

What We Know

We know that medium drusen are one of the first changes that indicate an eye is developing early AMD, and thus is at risk for going on to develop late AMD and visual loss. Drusen volumes are one of the parameters that can fluctuate, on average, but...

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Dr. Abdelfattah is a senior postdoctoral research fellow at Doheny Eye Institute. He has no relationships to disclose.
tend to increase over time.

Multiple epidemiological studies and clinical trials have evaluated phenotypic risk factors for the development of late or advanced AMD, defined as the development of CNV or central demyelinating atrophy. These major risk factors include the presence of large drusen, larger drusen areas, subretinal drusenoid deposits and pigmentary alterations. These features have been incorporated into various scales to predict the risk of developing advanced AMD over time. These features, however, were based on and restricted by the types of analyses that were possible using flash color film photography. Flash color photographs also identified atrophy, basing its presence on a triad of features: depigmentation, increased visibility of choroidal blood vessels and sharply demarcated borders. Reliable identification of atrophy, however, depended on good quality imaging with excellent stereopsis. Subsequently, researchers have moved to using fundus autofluorescence (FAF) imaging to identify atrophy because it provides better contrast and is less dependent on image quality, but clinical trials of wet AMD have not used this tool thus far.

Identifying atrophy in the setting of neovascular AMD is at least one step more difficult due to the potential obscuring features of the CNV and associated exudative process. To most precisely study atrophy in this setting and also attempt to isolate the specific impact of anti-VEGF therapy on atrophy, one would focus on atrophic lesions that are separate from and non-adjacent to the CNV lesion. Unfortunately, the challenge to such an approach is that the CNV lesion may grow over time and eventually include the originally non-adjacent areas. Another challenge is that most studies define the CNV lesion based on a fluorescein angiogram (FA), whereas the true/full extent of the lesion may be found to extend farther when one scrutinizes the optical coherence tomography (OCT) scans of these eyes.

**Atrophy-Therapy Relationship**

To better understand the characteristics and possible causes of vision loss in patients receiving anti-VEGF therapy, Philip Rosenfeld, MD, PhD, and colleagues retrospectively reviewed data from the Phase III ANCHOR and MARINA trials. They reported that 10 percent of study subjects who received monthly ranibizumab (Lucentis, Genentech) injections lost 15 or more letters of visual acuity (VA) over the course of 24 months. By comparison, 38 percent of patients in ANCHOR and 30 percent in MARINA gained at least 15 lines of vision in 24 months.

In both trials, vision loss was associated with retinal pigment epithelium (RPE) abnormalities and growth of total lesion area. But these lesions didn’t look like typical advanced wet AMD; rather, they looked more like lesions that the authors speculated might evolve into geographic atrophy (GA).

The reason photoreceptor loss occurs in patients who lose vision in the absence of active CNV or the more typical fibrotic scars seen in neovascular AMD is not yet known. Several hypotheses propose that perhaps photoreceptor loss occurs in some treated lesions when the neovascularization serves an important function to sustain the diseased macula. Once the neovascularization is suppressed, the nutritional support is eliminated and the outer retina degenerates. This type of outer retinal degeneration may be similar to the typical disease progression observed in dry AMD in the absence of neovascularization. Another possibility is that VEGF serves an important neuroprotective role and suppression of VEGF eliminates this neuroprotection, which may result in vision loss in those patients who are more susceptible to the loss of VEGF.

In the Comparison of Age-related Macular Degeneration Treatments Trials (CATT), which compared bevazucizumab (Avastin, Genentech) and
ranibizumab, investigators evaluated atrophy using color photographs and FA, but not the OCT. The found atrophy in 10.6 percent of subjects by the end of the first year, and in 18.3 percent by the end of second year. At two years of follow-up, the vast majority of patients with GA had extrafoveal GA (83 percent), whereas 32 patients (17 percent) had foveal GA.

One wonders, however, whether these extrafoveal GA patients would grow subfoveally if given enough time. According to the CATT trial, these characteristics were associated with increased risk for developing GA: visual acuity worse than 20/200, retinal angiomatous proliferation, GA in the fellow eye or intraretinal fluid at the foveal center at baseline. CATT showed that GA progressed faster in cases with classic CNV, GA in the fellow eye, ranibizumab therapy, non-subfoveal CNV, greater distance from foveal center and epiretinal membrane.

**What Other Studies Tell Us**

The Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial used OCT to evaluate atrophy. The difference in rates of atrophy between bevacizumab and ranibizumab was not statistically significant while similar to CATT. Continuous therapy caused more statistically significant atrophy than as needed therapy.

The HARBOR study retrospectively regraded FA and color fundus photography data for the presence of atrophy. HARBOR investigators defined atrophy as well-defined areas of depigmentation with visible, increased choroidal vessels (a minimum of 250 µm) corresponding to flat areas of well-demarcated staining on FA. They did not include cases of atrophy with RPE tears. The HARBOR reading center investigators attempted to distinguish whether the atrophy was non-adjacent to the lesion. They included all atrophy immediately within, adjacent to and non-adjacent to CNV lesions. Their results, based on the inclusive definition, were the most comparable to CATT and IVAN studies.

Among study eyes with no detectable atrophy at baseline, CATT showed a 20 percent rate of atrophy in ranibizumab-treated eyes by month 14. In the IVAN trial, this rate was 28 percent and in HARBOR, 29 percent.

Regarding visual outcomes, patients with baseline macular atrophy gained 6.7 ETDRS letters versus 9.1 letters for those without atrophy. Important to note is that in the MARINA study, untreated control patients lost 14.9 ETDRS letters after 24 months from baseline.

In HARBOR, eyes with and without concurrent atrophy had similar best-corrected visual acuity at each visit. Eyes that had intraretinal cysts or atrophy in the fellow eye at baseline were at higher risk of developing macular atrophy (MA). Interestingly, eyes with subretinal fluid (SRF) at baseline were at lower risk for developing MA. When looking at individual time points, less atrophy was detected in eyes with concurrent SRF, but patients with SRF were being treated per protocol in HARBOR to achieve the observed visual outcomes.

Higher doses of ranibizumab were not associated with an increased risk of MA, while monthly treatments (particularly at the FDA-cleared 0.5-mg dose) were associated with a higher risk of MA compared with as-needed therapy.

When considering the results of these studies, one must consider their limitations. The HARBOR analysis, for example, was a post-hoc retrospective assessment. While the plan to look for atrophy was pre-specified in CATT and IVAN, it is not clear if the study design pre-specified whether the details of how the cases would be graded and atrophy would be assessed. In addition, CATT re-assessed the presence and growth of atrophy multiple times, reflecting the difficulty of assessing atrophy in the setting of wet AMD using color photos and FA.

**Importance Of Fundus Autofluorescence imaging**

All of these studies may benefit from a re-assessment of atrophy based on eventual consensus definitions and a multimodal approach that integrates information from all
had evidence of decrease autofluorescence, which made them worse off than their entry visit into MARINA and ANCHOR. In addition, all of these patients had evidence of decrease autofluorescence on FAF imaging, with the vast majority having foveal involvement. Decreased autofluorescence on FAF imaging will show all areas of loss of RPE and photoreceptors, and thus will include not only areas of typical “atrophy” but also areas of fibrosis. From a patient’s perspective, whether atrophy or fibrosis causes photoreceptor loss may be irrelevant. Thus, the defect that FAF imaging measures may ultimately prove to be the best tool for studying outcomes in patients with wet AMD.

To summarize what we know: We know that patients with wet AMD can go on to lose vision over time and atrophy can be an important cause of this. We know that atrophy can occur in spite of anti-VEGF therapy. We know that the consistent risk factors for atrophy include the presence of intraretinal fluid and atrophy in the fellow eye. Continuous monthly therapy also appears to be associated with a higher rate of atrophy at least by two years.

Interestingly, subretinal fluid seems to be associated with a lower risk of atrophy. However, patients with subretinal fluid were still being treated in these studies to achieve the observed outcomes. We know that despite development of atrophy, patients still gain vision through at least 24 months, and we know from history that untreated patients lose considerable vision.

What We Don’t Know

Despite all of this information, we still don’t know if anti-VEGF therapy actually influences the development of atrophy in neovascular AMD. We also don’t know if the patients who had visual improvement despite the development of atrophy would eventually go on to lose vision over time. We don’t know if patients who are treated with the treat-and-extend regimen would develop rates of atrophy similar to monthly or as-needed (p.r.n.) therapy or somewhere in between. We also don’t know if we are detecting atrophy properly with the best definitions and methodology.

So What Should We Do With What We Do Know?

Given that none of these studies was designed to address the question of whether anti-VEGF therapy has an impact on development of atrophy, the observations so far really should not drive changes in how we treat patients. For example, leaving a patient with active disease untreated for fear of atrophy would appear to be unwarranted, and potentially harmful.

The data do suggest, however, that we should counsel patients that treating their wet AMD may not stop progression of their underlying dry AMD, and that they are still at risk for losing vision in the long term. Because the visual outcomes for p.r.n. and monthly therapy are similar, the observation of more atrophy with monthly therapy may lean toward using a p.r.n. strategy until better data are available.

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The use of anti-vascular endothelial growth factor (anti-VEGF) agents has resulted in a dramatic increase in intravitreal injections in recent years. An analysis of the Medicare claims database revealed fewer than 5,000 intravitreal injections in 2001 and 812,413 in 2007. Today, intravitreal injection (Figure 1) is one of the most commonly performed medical procedures in the United States. More than 2.3 million intravitreal injections were performed in the United States in 2012, and projections call for more than 6 million annually by 2016.

**Quantifying Risk Of Endophthalmitis**

With the widespread use of the intravitreal injection technique has come an increased concern regarding the risk of post-injection endophthalmitis. Because most patients treated with anti-VEGF agents receive a series of injections over months or years, it is important to distinguish between per-injection rates of endophthalmitis versus per-patient (or cumulative) rates of endophthalmitis over the course of treatment. While reported per-injection rates of endophthalmitis are generally very low in series of patients treated with anti-VEGF agents, per-patient rates may be close to 1 percent over a two-year course of therapy.

Recent series from Florida (20 cases of endophthalmitis out of 121,285 intravitreal injections, or a rate of 0.016 percent), Denmark (two cases out of 7,584 injections, or a rate of 0.026 percent), Australia (two cases out of 9,162 injections, 0.022 percent) and Massachusetts (three cases out of 10,208 injections, 0.029 percent) indicate an endophthalmitis rate of 1 per 3,000 intravitreal anti-VEGF injections or less. A population-based study in the United Kingdom estimated the per-injection rate of endophthalmitis following intravitreal anti-VEGF injections to be 0.025 percent. A review of the United States Medicare claims database revealed a per-injection rate of 0.09 percent for endophthalmitis associated with intravitreal anti-VEGF injections administered to patients with age-related macular degeneration (AMD).

In the Comparison of Age-related Macular Degeneration Treatments Trials (CATT), a prospective, mul-

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Dr. Flynn is the J. Donald M. Gass Distinguished Chair and professor of ophthalmology at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. He has no disclosures to report.
ticenter, randomized clinical trial comparing intravitreal ranibizumab (Lucentis, Genentech) and intravitreal bevacizumab (Avastin, Genentech) in 1,107 patients with neovascular AMD, the per-patient rate of endophthalmitis over two years was 0.7 percent with intravitreal ranibizumab and 1.2 percent with intravitreal bevacizumab ($p=0.38$). A meta-analysis of 43 studies reported that endophthalmitis occurred after 197 of 350,535 intravitreal anti-VEGF injections, a rate of 0.056 percent.\(^9\)

While most postsurgical endophthalmitis cases are believed to be related to the patient’s ocular surface flora, with the most common causative organisms being coagulase-negative \textit{Staphylococcus} species,\(^{11-14}\) many cases of endophthalmitis associated with intravitreal injection may be related to droplet transmission from the patient or from the health care providers involved with the intravitreal injection. \textit{Streptococcus} species, which comprise at least 41 percent of culturable adult salivary flora,\(^{15,16}\) are believed to contaminate operative fields by aerosolization or droplet spread.\(^{17-21}\) Several studies have reported that \textit{Streptococcus} species are significantly more likely to be the causative organism of endophthalmitis after intravitreal injection than after intraocular surgery.

Colin McCannel, MD, at Jules Stein Eye Institute at UCLA, summarized 54 cases of endophthalmitis following 105,532 intravitreal injections of anti-VEGF agents, and found that, of the culture-positive cases, \textit{Staphylococcus} (n=17, 65 percent) and \textit{Streptococcus} (n=8, 31 percent) were the most common causative organisms.\(^{22}\)

In contrast, in case series of postsurgical endophthalmitis, the proportion of culture-positive cases attributed to \textit{Streptococcus} species ranged from 0 to 9 percent.\(^{22}\)

Similarly, Ninel Z. Gregori, MD, and colleagues at Bascom Palmer Eye Institute reported on a series of 20 patients with endophthalmitis after 121,285 intravitreal injections of anti-VEGF agents.\(^3\) Of the nine (45 percent) culture-positive cases, five (56 percent) were \textit{Streptococcus} species, three (33 percent) were coagulase-negative \textit{Staphylococcus} and one (11 percent) was \textit{Bacillus anthracis}.

John B. Fileta, MD, and colleagues at Penn State College of Medicine reported a meta-analysis which included 197 cases of endophthalmitis out of 350,535 intravitreal anti-VEGF injections.\(^{10}\) The most commonly isolated organisms were coagulase-negative \textit{Staphylococcus} (38 percent) and \textit{Streptococcus} (29 percent). An analysis of conjunctival flora in patients undergoing intravitreal injections identified \textit{Streptococcus} species in only three of 71 cultured isolates (4.2 percent), supporting the hypothesis that such organisms come from respiratory droplets instead of the patient’s conjunctival flora.\(^{21}\)

### Strategies to Reduce Risks

Strategies that may be important in reducing the risk of complications associated with intravitreal injections include attention to issues before, during and after the injection. Tables 1 and 2 summarize intravitreal injection procedure guidelines developed as a result of expert committee deliberations conducted after a review of published and unpublished studies.

### Table 1. Guideline Areas with General Agreement Among Committee Members\(^{24}\)

- Povidone-iodine (5-10 percent) should be the last agent applied to the intended injection site before injection. If a gel anesthetic is used, povidone-iodine should be applied both before and after gel application, because retained gel may prevent povidone-iodine from contacting the conjunctival surface of the injection site.
- Topical antibiotics pre-, peri- or postinjection are unnecessary.
- No evidence supports the routine use of a sterile drape.
- Avoid contamination of the needle and injection site by the eyelashes or the eyelid margins.
- Avoid extensive massage of the eyelids either pre- or postinjection (to avoid meibomian gland expression).
- Use adequate anesthetic for a given patient (topical drops, gel and/or subconjunctival injection).
- Use sterile or nonsterile gloves as consistent with modern office practice, combined with strong agreement regarding the need for hand washing before and after patient contact.
- Either surgical masks should be used or both the patient and providers should minimize speaking during the injection preparation and procedure to limit aerosolized droplets containing oral contaminants from the patient and/or provider.
- Monitor IOP both pre- and post-injection.
- Routine anterior chamber paracentesis is not recommended.

and case series. Table 3 provides an appropriate sequence of events for the administration of intravitreal injection.24

An active external infection, including significant blepharitis, should be treated prior to injection. In addition, eyelid abnormalities such as ectropion have been reported as risk factors for endophthalmitis. Ocular surface bacteria represent an important source of bacteria-causing postoperative endophthalmitis11-14 and postintravitreal injection endophthalmitis.10,22

Thus, one strategy to reduce the risk of endophthalmitis is to reduce or eliminate the bacteria on the patient’s ocular surface and eyelids. While this may be achieved in various ways (povidone-iodine, topical antibiotics, eyelid hygiene and sterile isolation of the surgical site), povidone-iodine (Figure 2) is the agent that has been demonstrated to reduce the risk of postoperative endophthalmitis in a prospective study of cataract surgery.25

Lid scrubs have been associated with a significant increase in bacterial flora, so avoid excessive eyelid manipulation prior to injection. Since true contact allergy to povidone-iodine is rare, and anaphylaxis after ophthalmic application of povidone-iodine has not been reported, a reported history of contact allergy to povidone-iodine can be verified with a skin patch test. Conjunctival exposure to 5 percent povidone-iodine for a period of 30 seconds achieves a significant reduction in the bacterial colony-forming units and appears to be an adequate contact time before intravitreal injection.26

Antibiotics: No Proven Effect

Topical antibiotics have been demonstrated to reduce ocular surface bacteria, but have not been proven to reduce the risk of endophthalmitis.27-30 Despite evidence that topical antibiotics reduce the conjunctival bacterial load,29,31,32 several studies have demonstrated that the addition of preinjection or postinjection topical antibiotics to povidone-iodine antisepsis does not decrease the rates of endophthalmitis compared with the use of povidone-iodine alone.33-35

A prospective study that analyzed bacterial growth from conjunctival swabs reached a similar conclusion, preoperative application of moxifloxacin 0.5% offered no reduction in bacterial cultures beyond that of povidone-iodine alone.36

Moreover, use of topical antibiotics has been associated with increased bacterial resistance rates of ocular surface flora in patients undergoing intravitreal injections.27-30

In one prospective study over a one-year period, coagulase-negative Staphylococcus resistance to gatifloxacin and moxifloxacin roughly doubled, from rates of 39 percent and 34 percent, respectively, prior to intravitreal injections, to 67 percent and 70 percent, respectively, following treatment.37,38 These eyes were initially treatment-naïve, and all received four monthly intravitreal injections, followed by intravitreal injections as needed.

After each injection, patients were administered one drop of their assigned fluoroquinolone to the injected eye and were instructed to instill one drop of the fluoroquinolone q.i.d. for four days. Over the same one-year study period, untreated fellow eyes of the same patients did not develop an increase in fluoroquinolone-resistant coagulase-negative Staphylococcus strains. Thus, due to emerging antimicrobial resistance and lack of evidence supporting a reduction in endophthalmitis rates, topical antibiotic use for prophylaxis of endophthalmitis following intravitreal injection is not the current standard of care.

Other Preventative Measures

Because of the evidence that the underlying causative mechanism for some cases of endophthalmitis after intravitreal injection might be related to respiratory droplet transmission from the patient or the health-care providers involved with the injection,
an expert panel recommended the patient and providers either wear surgical masks or minimize speaking during injection preparation and the procedure.24,40

Another strategy involves the use of a sterile lid speculum during the injection procedure to avoid needle contact with lids and lashes. However, the most recent “guidelines” paper listed the use of a lid speculum as having “no consensus” among the panel members because many no longer used a speculum.24 The use of a sterile drape is also optional, but gloves, part of universal precautions, are appropriate. However, some panelists on the expert committee prefer to not use gloves.

The first step involves administration of a sterile topical anesthetic. Retina specialists may consider subconjunctival anesthesia, but this requires additional instrumentation and manipulation that may be associated with increased surface flora. If subconjunctival anesthesia is used, keep in mind that the needle used for intravitreal injection passes through the subconjunctival space filled with anesthetic and that surface bacteria may have been introduced beneath the conjunctiva. Although lidocaine gel has been known to improve patient comfort during intravitreal injections, it may also serve as a barrier, reducing the ability of povidone-iodine to contact the ocular surface and reduce the risk of endophthalmitis. Even if povidone-iodine is administered prior to lidocaine gel (in an attempt to bypass the potential barrier effect), one should recognize that the commercially available lidocaine gel is not prepared as a sterile formulation and, therefore, the injection needle may become contaminated as it passes through the lidocaine gel and before it enters the intravitreal cavity. Thus, if a gel anesthetic is used, povidone-iodine should be applied both before and after the gel. Care should be taken to avoid pressure to the eyelids, eyelid margins and the adnexa due to the potential for release of resident bacteria.
Approach with the Needle

Intravitreal injections should be given between the horizontal and vertical rectus muscles at the pars plana (Figure 3), 3.5 to 4 mm posterior to the limbus in phakic eyes and 3 to 3.5 mm posterior to the limbus in pseudophakic or aphakic eyes.

While the inferotemporal quadrant is generally the preferred site of injection due to such factors as ease of exposure (no need to pass the needle over the bridge of the nose or the brow), patient-specific considerations and the injecting physician’s preference should dictate quadrant selection. Although oblique and tunneled needle insertions have been described as attempts to minimize drug reflux after injection, a perpendicular injection approach is convenient and preferred in most settings.24 Needle gauge is selected based on the drug being injected. A 30-gauge or smaller needle is generally preferred for nonviscous drugs. Larger gauge needles may be considered for suspensions and for more viscous solutions. Needle length should be 5/8 inch (18 mm) or shorter, but long enough to permit complete penetration of the pars plana.24

The intraocular pressure (IOP) should be monitored postinjection and therapy for elevated IOP administered as indicated. Before the patient leaves the office, the injecting physician should assess IOP or confirm the presence of formed vision and give the patient 24-hour emergency contact information.

Patients and/or caregivers also need to be educated about the importance of avoiding eye rubbing and how to recognize and report immediately the signs and symptoms of endophthalmitis, retinal detachment and intraocular hemorrhage.

Conclusion

To optimize the outcomes associated with intravitreal injection, the retina specialist and staff should pay careful attention to reducing the risk of complications. Treatment outcomes depend not only on the safety and efficacy of the pharmacotherapy being delivered, but also on the safety and potential adverse events associated with the procedure itself.26

REFERENCES

Age-related macular degeneration is considered a complex genetic disorder, which means that multiple genetic variants contribute incrementally to disease risk, and environmental factors also play a role in its pathogenesis. Age-related macular degeneration (AMD) is also one of the best genetically characterized of all diseases, with more than 30 loci identified, accounting for a substantial proportion of the heritability. Variants in the complement factor H (CFH) and LOC387715/ARMS2 (Age-Related Maculopathy Susceptibility 2) loci have the strongest effect on AMD development and progression, but variations in many other genes also contribute to the disease.

The identification of these genetic loci has implicated several biological pathways in pathogenesis, such as the complement pathway, pathways for cholesterol and lipid metabolism, extracellular/collagen matrix, oxidative stress and angiogenesis signaling. In fact, AMD has become the paradigm for genetic discovery for complex disease with genetic loci discovered with family-based linkage studies, genome-wide association studies and next-generation sequencing approaches.

Genetic Polymorphisms In AMD

The discovery of genetic polymorphisms in AMD not only provided important insights to the disease pathogenesis, but also promises to change clinical practice. Genetic polymorphisms have a potential impact on risk stratification and predicting therapy response.

Genetic information improves the clinician’s ability to predict progression to the advanced forms of AMD, choroidal neovascularization and geographic atrophy above and beyond the information garnered from macular findings and demographic and behavioral risk factors such as...
age, sex, smoking and education. A risk prediction model with 10 single nucleotide polymorphisms (SNPs) in eight different genes was highly predictive of progression with an area under the curve (AUC) of 91 percent. The genetic component of the model added approximately 10 percent to the AUC when compared to a model with macular phenotypes and demographic/environmental risk factors alone.

Because of the genetic discoveries in AMD, genetic tests specifically for AMD are now widely available through physicians’ offices and in direct-to-consumer (DTC) packaging. Individuals can submit their DNA samples to a laboratory and receive information regarding their risk of AMD and many other diseases.

In 2014, the American Academy of Ophthalmology (AAO) published recommendations for genetic testing of AMD, and specifically recommended to “avoid routine genetic testing for genetically complex disorders like AMD… until specific treatment or surveillance strategies have been shown in one or more published prospective clinical trials to be of benefit to individuals with specific disease-associated genotypes.”

The wide availability of genetic tests for AMD raises many questions. Many studies have investigated the differential benefits of specific AMD treatments based on genotypes, but do they meet the AAO standard on routine genetic testing? Are existing DTC genetic tests accurate and reliable to help patients obtain useful information about their individual risk of a complex genetic disease?

This article aims to summarize the current literature on AMD pharmacogenetics, provide an overview of DTC genetic testing, and touch upon important considerations when retina specialists encounter patients interested in commercial genetic testing for AMD.

### The Evidence Regarding AREDS

The results of the Age-Related Eye Disease Study (AREDS) trial showed that supplements containing antioxidant vitamins plus zinc significantly reduced the odds of developing advanced AMD in patients with extensive intermediate size drusen, at least one large druse or noncentral geographic atrophy in one or both eyes. Eleven patients would need to be treated for seven years to prevent progression in one. From a public health perspective, investigators reported that if 8 million individuals at high risk for advanced AMD received treatment with the AREDS formulation, more than 300,000 would avoid disease progression and vision loss.

In 2013, the AREDS2 trial found that beta carotene was associated with a higher incidence of lung cancers in former smokers and that an alternative regimen that substituted lutein and zeaxanthin for beta-carotene, was as effective in reducing the risk of developing advanced AMD. Recently, several studies have looked at the influence of genotypes on treatment response to AREDS vitamin supplementation. CFH (Y420H, rs1061170) and LOC387715/ARMS2 (A69S, rs10490924) were the two genetic loci the studies focused on because they both have strong effect sizes.

### Table 1. Studies of CFH Genotype Response To AREDS Supplementation in AMD

<table>
<thead>
<tr>
<th>Studies of CFH and ARMS2 Genotype</th>
<th>No. of Subjects</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michael Klein, MD, et al. 200811</td>
<td>876</td>
<td>All genotype groups benefited although CFH high risk benefited less, may be driven by zinc component.</td>
</tr>
<tr>
<td>Johanna Seddon, MD, et al. 200912</td>
<td>1,446</td>
<td>Benefit of antioxidant-mineral supplement with the CFH homozygous low-risk genotype, but no benefit for homozygous risk genotype.</td>
</tr>
<tr>
<td>Johanna Seddon, MD, et al. 201113</td>
<td>2,937</td>
<td>Benefit of antioxidant-mineral supplement with the CFH homozygous low risk genotype, but no benefit for homozygous risk genotype.</td>
</tr>
<tr>
<td>Carl Awh, MD, et al. 201314</td>
<td>989</td>
<td>Differences in patients according to genotype: • Some genotypes showed no benefit of any supplementation • Some genotypes did better with zinc only or antioxidants only</td>
</tr>
<tr>
<td>Emily Chew, MD, et al. 201415</td>
<td>1,413</td>
<td>CFH and ARMS2 genotypes do not alter benefit of AREDS supplements</td>
</tr>
<tr>
<td>Carl Awh, MD, et al. 201516</td>
<td>989</td>
<td>Certain genotype groups had neutral or unfavorable responses (progression to advanced AMD) with supplements.</td>
</tr>
<tr>
<td>Emily Chew, MD, et al. 201517</td>
<td>526</td>
<td>In independent sample, results of Dr. Awh et al (2015) were not replicated</td>
</tr>
</tbody>
</table>

**KEY:** AREDS = Age-Related Eye Disease Study; ARMS2 = age-related maculopathy susceptibility 2; CFH = complement factor H.
and are related to progression from early and intermediate AMD to advanced stages in the AREDS cohort. The studies found conflicting results, particularly around the interaction between CFH genotypes and zinc supplementation. The studies have investigated different patient subsets enrolled in the original AREDS trial.

In the first study of pharmacoge

etries related to the AREDS formula

tion, Michael Klein, MD, and col

leagues in 2008 evaluated 876 in

dividuals with intermediate or uni

lateral advanced AMD at baseline (Table 1). They assigned patients to four treatment groups: placebo (n=204), antioxidants alone (n=219), zinc alone (n=217), or antioxidants and zinc (n=236).

The investigators found evidence of a possible interaction between CFH genotype and treatment with zinc—specifically, that participants who were homozygous for the non-risk allele (TT) at CFH loci had greater reduction in AMD progression than individuals with risk alleles (CC), 68 percent versus 11 percent, when treated with antioxidants and zinc instead of placebo (p=0.03). They also found positive interaction between zinc supplementation and CFH genotype (p=0.004).

However, Dr. Klein and colleagues also found that all groups, including patients with high-risk CFH alleles, benefited from AREDS supplementation. They concluded that genetic testing was not indicated because supplementation benefited every group to some degree.

**Controversies in AREDS**

Johanna Seddon, MD, MSc, and colleagues in 2009 and 2011 expanded their previous analyses in 2007 and 2008, and published risk progression models for progression to AMD, and both analyses showed positive interactions between CFH genotype and treatment groups (Table 1). In particular, these models showed that combined antioxidant-zinc supplementation derived a greater benefit than placebo for subjects with the homozygous non-risk genotype, but the benefit did not extend to the those with the homozygous risk genotype. The study did not find any interactions between antioxidant/mineral supplements and other genetic variants.

Carl Awh, MD, and colleagues reported findings in 2013 that were consistent in some respects with the previous reports, but also brought into question the effectiveness of AREDS formulation in patients with different genotypes (Table 1). This study included patients with AREDS category 3 disease in at least one eye. These authors found a positive interaction between placebo vs. zinc treatment groups and CFH risk alleles. They also reported that patients homozygous for CFH risk alleles and without ARMS risk alleles treated with zinc had a 43 percent greater progression rate by 12 years compared with those treated with placebo.

Dr. Awh's group estimated that these patients could have a 56 percent reduction of 10-year progression to advanced disease with antioxidants alone rather than the AREDS formulation. Individuals with one CFH risk allele and no ARMS2 risk alleles could have a 29 percent reduction in progression rate with antioxidants rather than the AREDS formulation.

Based on these findings, the authors recommended treating patients with different nutritional supplements based on their genotypes. Limitations for which this study was criticized were selective subgroup post-hoc analysis and testing multiple hypotheses without sufficient correction for multiple testing.

After these studies Emily Chew, MD, of the National Eye Institute led a study examining 1,413 AREDS participants for whom genotyping was available. This investigation concluded that no interactions existed between genotypes and AREDS supplementation (p=0.06, Table 1). One critique of this study was that it was significantly underpowered to evaluate certain subgroups for clinically important interactions; certain subgroup analyses had fewer than 10 patients.

More recently, Dr. Awh's team published another analysis with the same 989 participants from their original article. Again, they found positive interactions between zinc and AREDS treatment with the genotypes (Table 1). They also found that patients with two CFH risk alleles and no ARMS2 risk alleles progressed more with zinc-containing treatment than with placebo, with a hazard ratio of 3.07 (p=0.0196) for zinc and 2.73 (p=0.0418) for AREDS formulation.

For patients with zero or one CFH risk alleles and no ARMS2 risk alleles, neither zinc nor AREDS altered progression of disease compared to placebo, while antioxidants decreased progression.

For patients with two CFH risk alleles and one or two ARMS2 risk alleles, no treatment was better than placebo. The authors concluded that the benefit of the AREDS formulation was a result of favorable response by patients in only one genotype group, balanced by neutral or unfavorable responses in three other genotype groups.

Simultaneously, Dr. Chew and
her group published an analysis that used Dr. Awh’s methods but applied them to a different cohort of 526 AREDS patients. The results varied significantly from those Dr. Awh’s group reported.

Specifically, in the group with zero or one CFH risk alleles and no ARMS2 risk alleles, the residual cohort showed a marked beneficial treatment effect of the AREDS supplement and a smaller beneficial effect of zinc. In contrast, for this same genotype, Dr. Awh’s group found that only antioxidant supplementation was beneficial.

Participants in the residual cohort with two CFH risk alleles and no ARMS2 risk alleles also benefited from AREDS supplements—again, in contrast with the 2.73-fold increase in progression seen in the cohort in Dr. Awh’s report.

Dr. Chew and her associates found that all four genotype groups in the residual cohort benefited from the AREDS combination of antioxidant and zinc. They could not replicate the results from Dr. Awh’s group using the residual cohort, and suggested that Dr. Awh’s findings were likely false positives due to the multiplicity of genetic subgroups examined, the large number of potential comparisons without sufficient correction of the p values and the lack of a pre-specified hypothesis.

**Why Comparisons Are Difficult**

The different analytic approaches of the initial studies examining response to AREDS supplementation by genotype make it difficult to compare them directly. We can say that the earlier analyses indicated that some interaction may exist between zinc supplementation and CFH genotype. However, identical analytic methods could not replicate this in a different independent, although relatively small sample.

The initial findings were also based on post-hoc subgroup analyses and, thus, do not meet the AAO criteria for data from a prospective study to prove the clinical utility of genetic testing. So the evidence currently is not sufficient to warrant genetic testing for decision-making regarding AREDS supplementation. However, initial studies on this topic are suggestive of an interaction, so this cannot be ruled out.

Worth noting is that genetic testing is currently recommended for ocular diseases, such as retinal degenerations that are considered to be Mendelian genetic disorders. In Mendelian conditions, a mutation in one gene is generally sufficient to cause disease, and environmental factors to date have not been shown to play a major role in disease development.

**Pharmacogenetics Of Anti-VEGF Agents**

Small studies have shown a potential differential response of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents for wet AMD according to genotype, but
larger, well-powered trials have not. Most data from smaller studies supported that having risk alleles at the CFH Y402H and ARMS2 loci were associated with worse visual outcome after anti-VEGF therapy, thus requiring additional intravitreal injections.25–31 Also, some conflicting results have reported that higher-risk genotypes at CFH and VEGF genetic loci were associated with better visual outcomes.25

However, the results of the better-powered and prospective Comparison of Age-related Macular Degeneration Treatment Trials (CATT) and Inhibition of VEGF in Age-related Choroidal Neovascularization (IVAN) study found no significant associations between any genetic variants and response to anti-VEGF therapy.32–35 Prospective trials do not indicate that genetic testing is clinically informative when making decisions on anti-VEGF treatment.

Similarly, the data for pharmacogenetics of response to photodynamic therapy are also conflicting. Three studies showed no effect of CFH genotype on response to photodynamic therapy.26–28 One study showed better visual outcomes with high-risk alleles at the CFH loci,29 and another showed worse visual outcome with high-risk alleles.30 Studies have also investigated other genetic loci, such as the prothrombin gene, methylenetetrahydrofolate reductase, factor XIII-A, VEGF, and HTRA1, but these studies have involved modest numbers of patients and none of the reported associations has been consistently and independently replicated.33–36 Photodynamic therapy is rarely used for AMD today, so data may not ever exist to determine the usefulness of genetic testing for predicting response to this therapy.

Direct-to-Consumer Genetic Testing

While more evidence would be helpful to support physician-ordered genetic testing for AMD patients, some patients may pursue genetic testing on their own. Retina specialists need to be aware of the available tests so that we can counsel patients who present them with the results. The rise of the personal genomics industry can be traced back to 2007 with the launch of DTC services from deCODE genetics and 23andMe, a Google-backed startup.26 Since then, many genetic testing companies have launched DTC genetic tests, and AMD is one of the most commonly tested eye diseases among them.37

We compared and contrasted six DTC AMD genetic tests currently available to consumers in the United States for the following characteristics: DNA source, number of SNPs, specific single-nucleotide polymorphisms (SNPs) tested and cost (Table 2). The companies accept DNA samples in the form of blood, buckle swab or saliva. The number of SNPs varies between two and 15. A 2014 study by Gabriella Buitendijk and colleagues in the Netherlands evaluated the concordance of results from DTC AMD genetic tests by 23andMe, deCODE, Easy DNA and Genetic Testing Laboratories. They performed the genotype analysis in their own laboratory.38 They found considerable variation of estimated risks among the four commercial tests in the three tested individuals, from a 1.6-fold difference for overall relative risk to an up to 12-fold difference for lifetime risk.

In one individual, one of the four tests indicated a higher-than-average genetic risk for AMD while another showed a lower-than-average genetic risk. The difference of estimated risks between the commercial tests and the validated prediction model was also significant—1.4 percent to 16.1 percent in DTC tests versus 0.5 percent to 4.2 percent in a validated prediction model. The authors attributed this discrepancy to the testing of only a limited set of genetic markers, the suboptimal choice of reference population that does not accurately reflect the consumer’s ancestry and life expectancy, and the methodology applied for risk calculation.

A study that evaluated risks of a wide range of diseases showed that AUC values of DTC tests differed significantly among the diseases and among the different tests for common complex diseases.39 The authors even showed that the formulas one company used could lead to a predicted risk exceeding 100 percent in high-risk cases. Retina specialists should warn patients about these perils and possible inaccuracies of DTC genetic tests. Other genetic tests not evaluated in that study may be more accurate.

Conclusion

Genetic testing holds great promise in the care of AMD patients. The extensive genetic discovery and excellent risk-prediction models developed thus far are the first step. Prospective studies would be helpful to show that predicting increased disease risk will make a difference in AMD patient outcomes and to determine whether patients with various genotypes would benefit from interventions such as more frequent in-office examinations, more rigorous home monitoring of disease or counseling about the importance of behavioral modification.
If these interventions produce better patient outcomes, then more evidence would exist to justify clinical genetic testing, according to the AAO. A randomized trial, however, would be expensive and difficult to execute, due to the availability of lifestyle counseling and monitoring already in place for high-risk patients. Moreover, considerable evidence suggests that higher-risk genotypes increase rates of progression and subsequent visual loss among individuals with the same baseline phenotypes, and methods are now available to obtain this information for those who desire it. Also, treatment-genotype interaction is likely to be confirmed for some AMD treatments in the near future, which would alter the course of such studies.

AMD has a strong genetic component. Should family members have the opportunity to learn about their genetic risk? Should individuals at particularly high risk, with presence of both common and rare alleles, for example, be identified for family counseling about healthy lifestyles, or get ocular examinations, or receive any other type of counseling and care? Should industry be stratifying patients in clinical trials according to a composite score that includes genetic risk groups, to determine who will benefit most? Additional exciting research is underway that will hopefully answer these questions.

References
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As breakthrough therapies and management strategies, along with emerging imaging algorithms, give retina specialists more and better tools for treating retinal disease, investigators continue to push the envelope and take retinal disease management to the next level, as evidenced by the thousands of abstracts presented last month at ARVO 2015 in Denver.

Here we present 10 compelling posters and presentations. They include exploration of the role of platelet-derived growth factor (PDGF) in the management of age-related macular degeneration (AMD), treatment of central serous chorioretinopathy, an approach to type 2 macular telangiectasia (MacTel) management, novel retinal detachment repair ideas, the importance of wide field retinal imaging and the relationship between vascular endothelial growth factor (VEGF) inhibition and macular atrophy in neovascular AMD treatment. Some of the studies are pre-clinical, others involve established therapies.

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

PDGF, VEGF Inhibition
An orally active tyrosine kinase inhibitor that acts against all PDGF and VEGF subtypes stabilized vision without the need for rescue therapy in a multicenter, early stage trial. Thirty-five patients with wet AMD who had been treated previously received X-82 (Xcovery Vision Inc.) in six different doses, ranging from 50 mg every other day to 300 mg daily. Eighty-nine percent of the 27 subjects who completed the full 24-week study did not require any rescue therapy with ranibizumab (Lucentis, Genentech). Eight subjects—one who received 100 mg, five who received 200 mg and two who received 300 mg—experienced significant reductions in fluid on spectral-domain optical coherence tomography (SD-OCT) within the first few weeks of X-82 initiation.
ti-PDGF therapy. All the investigators disclosed commercial relationships with Xcovery.\textsuperscript{4904}

**Anti-VEGF therapy may benefit** many patients with advanced visual loss from neovascular AMD, a retrospective analysis of 1,410 consecutive cases showed. The authors, noting that most anti-VEGF trials excluded subjects with severe visual loss, aimed to evaluate the efficacy of anti-VEGF intravitreal injections in neovascular AMD patients with advanced visual loss at therapy initiation and identify predictive factors.

The study involved 134 cases with baseline vision of 20/200 or worse and no other visually limiting eye disease, and followed them for six months; 97 were followed for 12 months. Univariate analysis showed an association between retinal hemorrhage and greater improvement, while intraretinal fluid on OCT was associated with less improvement at 12 months. By multivariate analysis, poorer visual acuity at baseline was associated with greater visual improvement, as was a greater number of injections received.

Larger macular lesion size on fluorescein angiography correlated with worse visual acuity at six but not at 12 months by both univariate and multivariate analyses. Injection medication type did not influence outcome. The authors concluded that the number of injections, macular lesion size and other clinical abnormalities might influence outcomes. They had no relevant relationships to disclose.\textsuperscript{1903}

**RTH258 (Alcon) is an anti-VEGF medication** given by intravitreal injection that is smaller molecularly than existing anti-VEGF treatments, which may allow greater penetration of ocular tissue and less systemic anti-VEGF exposure. The Phase II OSPREY trial randomized 86 patients with neovascular AMD to repeated doses of RTH258 or aflibercept (Eylea, Regeneron). The trial found that RTH258 was not inferior and was well tolerated. Patients in both groups were comparable in terms of presence of intraocular hemorrhage, subfoveal choroidal neovascularization, subretinal fluid and intraretinal cystoid edema. All of the study participants disclosed relationships with Alcon.\textsuperscript{4901}

**As-needed treatment with ranibizumab** can maintain vision improvements in individuals with diabetic macular edema (DME), according to three-year results from an open-label extension of the RIDE/RISE trials. Patients were randomized to monthly ranibizumab 0.3 mg or 0.5 mg, or sham injections. Sham patients crossed over to monthly ranibizumab 0.5 mg after 24 months, and after 36 months participants were eligible to enter the open-label extension (OLE) study of ranibizumab 0.5 mg as needed.

Five hundred patients entered the OLE, receiving an average of 3.8 injections of ranibizumab 0.5 mg annually. Nearly 25 percent of patients did not require any further therapy during the OLE. Of 298 patients followed for more than a year, 19.5 percent required no further treatment. At 36 months, the 0.3 mg ranibizumab group showed an average gain of 12.4 letters in visual acuity, compared with 11.2 letters for the 0.5 mg group. Compared to their respective RISE/RIDE baselines. The study co-authors disclosed relationships with Genentech.\textsuperscript{5674}

**Chronic Central Serous Chorioretinopathy**

Photothermal therapy delivered by micropulse laser is safe and can improve visual acuity in the treatment of central serous chorioretinopathy (CSCR), and may have potential for treatment of other macular disorders, according to a study of 19 eyes using the PASCAL laser (Topcon) using EndPoint Management software. The investigators applied an average of 532 laser spots at 30 percent energy. All patients had persistent CSCR of longer than four months.

Participants received, on average, 2.2 treatments a year to manage recurrence fluid or incomplete resolution. They achieved an average gain of 12 letters at two months and sustained that through 12 months of follow-up. Central macular thickness decreased from 350 to 271 µm.

The investigators concluded that lack of tissue damage allows periodical retreatment without the cumulative scarring of conventional photocoagulation. They said this technique should be tested for the treatment of other macular disorders, and may even be combined with anti-VEGF treatments of macular pathology. All the investigators disclosed relationships with Topcon.\textsuperscript{5674}

**The mineralocorticoid receptor antagonists** spironolactone and eplerenone are effective for the treatment of treatment for CSCR, a randomized, placebo-controlled, crossover clinical trial showed. The study reported that spironolactone appeared to have better anatomic outcomes and achieved a faster resolution of subretinal fluid.

The trial included 30 patients with CSCR of at least three-months duration, randomized to three groups:

- 25 mg/day of oral spironolactone for a week then 50 mg/day for three weeks then 50 mg/day oral eplerenone for a month.
- 25 mg/day of oral eplerenone for a week then 50 mg/day for three weeks, then 50 mg/day of oral spironolactone for a month.
Repair of Retinal Pathology
An absorbable polyethylene glycol-based synthetic hydrogel sealant has been shown to seal retinal breaks and prevent experimental rhegmatogenous retinal detachment in rabbit eyes without intraocular tamponade. FocalSeal (Focal Inc.) is a liquid that polymerizes under visible xenon illumination, and forms a clear, flexible and adherent hydrogel. The investigators applied FocalSeal to entirely cover iatrogenic retinal breaks in three rabbit eyes and then polymerized the liquid with xenon light. They then performed air-fluid exchange and finished without intraocular tamponade. They did the same procedures in three other eyes but without FocalSeal.

Funduscopy showed that the retinas were reattached in all eyes of the FocalSeal group while all three eyes of the control group resulted in proliferative vitreoretinopathy. The investigators observed FocalSeal on the retinal breaks at one and seven days, but not after one month. None of the investigators had any relationships to disclose.

Type 2 Macular Telangiectasia
Early results of a ciliary neurotrophic factor (CNTF) implant for treatment of type 2 macular telangiectasia, known as MacTel, have shown no safety issues with the treatment, according to a non-randomized, Phase I, uncontrolled trial of seven patients who completed three years of study. None of the patients had neovascularization secondary to MacTel at enrollment or after three years, and imaging showed no significant progression of any MacTel characteristics. The mean retinal thickness in eyes with the CNTF implant showed a marked increase in ETDRS zones 6-9 (20-23 μm), while the untreated eyes showed less increase of 6-11 μm. By en-face imaging, the key regions of macular pathology did not change in either eye significantly during the trial.

The investigators described an ongoing Phase II trial to further evaluate safety and efficacy of CNTF in MacTel. The study authors had no conflicts to disclose.

The study found no differences for recovery time or postoperative difficulty between the three groups. The study received support from the National Heart, Lung and Blood Institute. The study authors had no other disclosures.

Imaging Analytics
A computer-based segmentation algorithm for ultra-widefield angiography can analyze ischemia and leakage in diabetic retinopathy and retinal venous occlusions (RVO). Investigators developed the algorithm to identify areas of leakage and ischemia with co-registration of the two image time points using ultra-widefield angiography by the 200Tx (Optos). They also performed manual segmentation with Image J software to validate the computerized algorithm. They quantified areas of ischemia relative to the overall retinal area, measured by an “ischemic index.” Similarly, they also quantified relative area of leakage, creating a “leakage index.”

The study included 32 eyes of 32 patients with diabetic retinopathy or RVO. The automated algorithm successfully analyzed all images. All eyes displayed macular and/or peripheral leakage, while only 18 eyes presented with ischemia. The average leakage index was 4.4 percent. Of the 18 eyes with ischemia, the mean ischemic index was 13.7 percent, most of which was peripheral.

Standard angiography may overlook pathology in the retinal periphery, the authors stated. Gaining a better understanding of the location of these features—in the far or mid-periphery or macula—may aid in evaluating disease burden, treatment response and prognosis, but more research is needed to enhance identification of leakage. None of the investigators had any relationship with Optos.
How to Supercharge Billing Functions

How quantitative accountability can improve cash flow.
By Alison Ratliff, MBA

The key to successful billing can be summarized in two words: quantitative accountability. It comes down to this: Does each member of your practice’s billing team have a responsibility, and can you measure her individual success? Solid billing applications can be the difference between a generally successful practice and the practice that performs at an even higher level.

Subdivide Into Financial Classes

The first step in optimizing performance of your billing department is to assign tasks by financial class—that is, assign specific tasks to each biller. This not only clearly delineates responsibilities, but it allows staff members to easily isolate problems. For example, if you have a department of eight and each has five denials on Anthem claims, individually they may not recognize a problem. However, if you one biller is assigned to post all Anthem claims and she sees all 40 denials, she will see the problem and be able to fix it and avoid significant financial disruption.

Your practice can be divided into as many or as few financial classes as the size of your payer demographic permits. For larger practices, I have found that the most dominant and easily identifiable classes are as follows: Medicare; Medicaid; Anthem; HMO; Blue Shield; Other Commercial Payers; and Workers Comp. Based on your payer population, you may need to divide these classes even further, perhaps dividing Anthem by alphabet, classifying your different Medicaid carriers or dividing “Other Commercial” into groups of your larger commercial carriers.

With some payers reducing filing deadlines to 90 days, it is imperative that billing departments stay current on submissions, appeals and follow-up. This is most important for drug reimbursements, as we strive to get paid in full before paying the large invoiced amounts.

The Theory of R-E-V-E-N-U-E

The old way of delineating job duties in billing departments between members who posted payments and those who worked reports provided very little quantitative accountability. We could not measure who was carrying their own weight and who was just along for the ride. So, we implemented a theory of R-E-V-E-N-U-E:

- Reporting:
- Reports, reports, reports;
- Expansion;
- Vesting;
- Expectations;
- No permissions for write-offs;
- Understanding;
- Evaluate.

Reports are instrumental in recording and measuring financial success. When you break a practice down into financial classes, reporting becomes more manageable and much more enticing to your team. Some items will generate small reports; more comprehensive items will demand more time.

Examples of key reports the practice should generate on a rotating weekly schedule are High-Dollar Drug, Low-Dollar Drug and High-Dollar Procedure Line Items. These three reports rotated over a...
month will capture your expensive pharmaceuticals, your more moderately priced but still hard cost drugs and your high-dollar procedures like lasers and surgeries. The end of the fourth week of the month can be set aside for the 90-day accounts receivable report. (The “Evaluate” section provides a more detailed explanation of time allocation.)

Expand

After you establish a baseline of each individual’s skill set, expand her responsibilities until you both feel satisfied that she’s working at maximum production. If one biller seems to complete the assigned work for her financial classes early, perhaps she can work on the “seen-and-not-billed” report, handle refund requests, reconcile the drug log or chart audit requests. Minimizing employee downtime by assigning additional tasks will not only reduce salary overhead, but also award your hard-working employees with further recognition within your practice.

Vesting

We all too often find fault within our billing departments for decreased payments, incorrect write-offs and incomplete drug reimbursements, but how often do we include billing staff in clinical successes? When drug logs are reconciled correctly, usually we applaud the scribes or techs. When the physician has a smooth day in clinic, she or he can be very complimentary.

Expectations

As leaders, we can all visualize what we expect of our team members, but often do not verbally express what our optimal outcome may look like. How can we gauge success or failure if we do not clearly define expectations at the start? More importantly, how can we hold others responsible for not meeting standards that were not clearly explained?

No Permissions for Write-Offs

Supervisors should be the only team members with the authority to permit significant write-offs beyond the standard insurance adjustments. A common practice has been to incentivize individuals based on keeping outstanding claim percentages below a target. However, if not carefully monitored and highly restricted, this can encourage unnecessary and improper claim write-offs to hit incentive goals.

Understanding

Require that each staff member have a comprehensive knowledge of reimbursement expectation for her financial class. Ask each person to prepare a fee schedule on a regular basis to ensure that she is always up to date with any changes or payer coding requests.

Evaluate

Direct the time allocated to each job function (posting, follow-up, reporting, etc.). I suggest setting the following daily time limits during implementation: one hour on the weekly report, two hours on accounts receivable and the remaining five hours on batch posting. By requesting that team members spend the same amount of time on each aspect of the job, you can properly evaluate their individual talents.

Understanding the Concept

Many times throughout my career, physicians have asked me to explain the billing process because they, in their own words, “just do not understand it.” I can relate, as I feel the same way about our information technology. You could talk to me all day about T-1 lines, bandwidth, megabytes up and down, and at the end of our discussion I would still have only a vague understanding of how it all works. For the sake of this discussion, I have simplified the billing process into the steps shown in the accompanying diagram on page 37.

If your entire team understands this process, they can begin to fill in the blanks on their own, leaving management to focus on more serious payer problems.

Conclusion

To fall back on the sports metaphor, all-star teams exist for a reason: no one team has all the “best of the best.” The team that wins the championship has some outstanding players working in combination with those regarded as good, average and, all too often, mediocre. Teams that go the farthest utilize players in their best positions, not necessarily the position they want to play or the one they’ve always played.

The mantra of doing something because that’s the way you’ve always done it has become much too common in departments such as billing. That would never work with a sports team, and we would never apply that mindset to patient care. Just as the clinical standard of care is continuously evolving, so too must our revenue-generating protocol. Quantitative accountability can get you there.

Ms. Ratliff is chief operating officer at California Retina Consultants and Research Foundation, Santa Barbara.
According to the American Medical Association, physicians have at their disposal more than 2,000 different types of genetic tests to aid in the diagnosis and treatment of more than 1,000 diseases. What do all these tests mean for retina specialists? I’ll provide some answers.

**Test Rationale**

As a response to the growing interest in genetic testing, the American Academy of Ophthalmology (AAO) revised a clinical statement, *Recommendations for Genetic Testing of Inherited Eye Diseases.* The AAO describes three advantages of pre-symptomatic genetic testing:

- It allows a physician to administer preventive therapy before clinically detectable damage occurs.
- The physician can also increase surveillance for treatable disease.
- And, at-risk individuals can make informed reproductive decisions before a disease is clinically detectable.

The AAO cautions against over-testing with bundled or parallel testing of many loci or genes. As the guideline states:

> A major issue with extensively parallel genetic testing (e.g., hundreds or thousands of genes) is the collateral discovery of numerous clinically relevant findings that are unrelated to a patient’s presenting symptoms. The chance of making such a discovery, and thereby incurring the responsibility for appropriate counseling and referral to other health care specialists, is proportional to the amount of the genome one assesses in each genetic test.

The AAO encourages standard medical evaluations and discourages routine genetic testing of complex disease and/or patients with a family history of complex disease until studies and trials support that testing.

Complex disorders (e.g., age-related macular degeneration and glaucoma) tend to be more common in the population than monogenic diseases and the presence of any one of the disease-associated variants is not highly predictive of the development of the disease … Until such benefit can be demonstrated, the routine genetic testing of patients with complex eye diseases, or unaffected patients with a family history of such diseases, is not warranted.

**Coverage**

In June 2012, the Office of the Inspector General published *Memo randum Report: Coverage and Payment for Genetic Laboratory Tests*, OEI-07-11-0011. This report references and applies the Social Security Act’s coverage mandate as follows:

> Since CMS [Centers for Medicare & Medicaid Services] considers predictive tests to be screening tests, genetic tests for this purpose are not covered by Medicare. However, genetic tests used to diagnose or determine treatment in the presence of signs and symptoms of disease can be covered by Medicare.

So, Medicare covers tests that provide useful information in treating an existing condition, but otherwise, CMS does not cover screening tests.

In the private sector, Aetna Clinical Policy Bulletin, *Glaucoma Testing* (No. 0622) discusses genetic testing. It states: “Aetna considers genotyping for the screening, diagnosis and monitoring of glaucoma experimental and investigational because of insufficient evidence of its effectiveness.”

(continued on page 40)
Coding and Reimbursement

The Current Procedural Terminology (CPT) manual contains Tier 1 and Tier 2 Molecular Pathology procedures. Codes described in the Tier 1 sequence of CPT codes (81200–81383) list gene-specific and genomic procedures. According to CPT, “molecular pathology procedures that are not specified in 81200–81383 should be reported using the appropriate Tier 2 code (81400–81408) or the unlisted molecular pathology code, 81479.” Following CPT instructions, Tier 2 codes represent medically useful procedures that are generally performed in lower volumes than Tier 1 procedures. Within the Tier 2 sequence, multiple tests specifically refer to numerous ophthalmic conditions (Table).

The table on page 39 is not a complete list of the genes; the National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE), a research venture of the National Eye Institute, provides a lengthy list of genes and diseases that could be considered for testing.

Both Tier 1 and 2 tests are subject to the Clinical Laboratory Improvement Amendments (CLIA) edits and require a CLIA certificate. In reviewing the 2015 Clinical Laboratory Fee Schedule, only Tier 1 codes have reimbursement rates.

For non-screening tests, current coverage and reimbursement for Tier 1 and 2 tests is spotty at best. As a practical matter, use an Advance Beneficiary Notice of Noncoverage prior to genetic testing until your Medicare administrative contractor establishes coverage guidelines.

Conclusion

The AAO advises caution with genetic testing, and recommends a focus on a specific disease rather than broad-spectrum testing. According to the AAO, your clinical examination is the best method for assessing and following disease. Coverage and payment for genetic testing depends on why and when it is performed. Reimbursement is spotty, so genetic testing in an ophthalmology practice is narrowly applicable due to its limited utility and restrictions on reimbursement.

REFERENCE


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JUNE

11-13
RETINA IN PROGRESS
Symposia Congressi, Florence, Italy
Contact: cristina.nava@symposiacongressi.eu
www.symposiacongressi.eu/symposia/congressi/11/EN/

28-30
MACULAR MEETING PARIS 2015
Eurouettes George V, Paris
Contact: macular2015@europe-organisation.com
www.macular-meeting.com

JULY

10
FOURTH ANNUAL COLE EYE INSTITUTE IMAGING SUMMIT
Hotel Imperial Vienna, Vienna, Austria
Contact: info@mcmeglobal.com

11-14
AMERICAN SOCIETY OF RETINA SPECIALIST 33RD ANNUAL MEETING
July 11-14
Contact: sam.zerang@asrs.org
www.asrs.org/annual-meeting

SEPTEMBER

12-14
15TH EUROPEAN VITREORETINAL SOCIETY MEETING
Venice, Italy
www.evers.eu

17-20
15TH EURETINA CONGRESS
Société d’Exploitation de Nice Acropolis, Nice, France
http://euretina.org/rice2015/programme/default.asp

OCTOBER

7-11
THE RETINA SOCIETY ANNUAL MEETING
HerContinental Paris – Le Grand, Paris
www.retinasociety.org/2015AnnualMeeting

NOVEMBER

13-17
AMERICAN ACADEMY OF OPHTHALMOLOGY 2015 RETINA SUBSPECIALTY DAY (13,14)
ANNUAL MEETING (14-17)
Sands Expo/Venetian, Las Vegas, Nev.
www.aao.org/meetings/annual_meeting/
Experience of 50 Vitrectomies with EVA

Smooth transition between vacuum and flow modes.

Switching from vacuum to flow mode during vitrectomy without changing pumps is something that retina specialists could only imagine in their wildest dreams, but with the EVA surgical system, they now have that capability literally at their fingertips, says Gaurav K. Shah, MD, co-director of retina fellowship at The Retina Institute and professor at Washington University in St. Louis.

Dr. Shah, who discloses that he is an advisory board member for Dutch Ophthalmic Research Center (DORC), the maker and distributor of EVA, has performed around 50 vitrectomies with EVA. Its VacuFlow VTI (for valve timing intelligence) pump system provides both flow and vacuum fluidics.

Fast Cutting, Even Suction

For Dr. Shah, the TDC cutting system, which stands for two-dimensional cutting, is well suited to the smaller-port 27-gauge surgery that more retina specialists are adopting. The TDC vitrectome cuts at speeds of up to 16,000 cycles per minute and has vacuum control that maintains even suction.

"With this technology you can do flow control that allows precision control with less movement of the retina, which is especially evident during retinal detachment," Dr. Shah says. "In flow control, the flow pushes individual pieces into the cutter; it gives you precision and you have to go to it, it doesn't come to you."

Flow control provides a higher level of accuracy when cutting the vitreous close to the retina surface. "That allows you to do very meticulous, precise shaving of the vitreous base," he says. The TDC vitrectome also cuts forward and backward without closing, Dr. Shah says. "This is a very different cutter."

Flow and Vacuum Modes

The ability to change between flow and vacuum modes also has its advantages, as Dr. Shah explains. "If you want to do entire case in vacuum you can. If you want to do an entire case in in flow, you can, or you can do a combination," he says.

"Typically, I do a core vitrectomy with vacuum mode and then as I move into the periphery, I will do that in flow mode."

The system does allow faster operative times. "But to me that's really not relevant whether it's three or five minutes less," Dr. Shah says. "We all want to look at outcomes of patients as more important than times."

EVA at a Glance

EVA is for both vitreoretinal and cataract surgery. The company says the flow mode can complete the fluid-air exchange without the drop in intraocular pressure that can occur because of the variation in viscosity between the balanced-salt solution and air. The vitrectome is available in 20 through 27 gauge. It uses LED illumination to minimize UV light exposure. A green 532-nm laser with a wireless foot pedal is optional.
Impact of the OHR-102 IMPACT Data

A closer look at combination therapy and CNV.

When Ohr Pharmaceutical Inc. announced the topline results from the Phase IIb IMPACT study evaluating OHR-102 (0.2% squalamine lactate ophthalmic solution) combination therapy with ranibizumab (Lucentis, Genentech) for the treatment of wet age-related macular degeneration (AMD), the company acknowledged the overall study failed to meet its primary endpoint.

However, 42 percent of the subgroup of patients with classic-containing choroidal neovascularization (CNV) on the combination therapy achieved three or more lines of vision improvement, compared with only 28 percent in the ranibizumab monotherapy arm. Ohr believes these data justify Phase III trials in wet AMD. Thomas A. Ciulla, MD, chief clinical investigator of IMPACT, answered questions via e-mail.

Q Can you describe the mechanism of action of OHR-102?
A Squalamine is a small-molecule drug, which has been shown to inhibit multiple angiogenic growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF). It does so through a novel intracellular mechanism, which involves uptake by active endothelial cells and binding and displacement of calmodulin. It simultaneously shuts down these growth factors, unlike current intravitreal retina medications, which inhibit the target via extracellular binding. Squalamine has been shown to inhibit ocular neovascularization in animal models.

Q Trials of topical agents for retinal disease have a history of failing. Why is this different?
A Squalamine was originally developed as an intravenous drug. In Phase II trials, it demonstrated a biological effect, a dose response and a visual acuity benefit. Due to its rapid clearance, pharmacokinetics and impractical delivery, it was not pursued further. While many previously studied topical agents for the treatment of retinal disease failed to show efficacy, OHR-102 is a proprietary formulation designed to improve trans-scleral permeability and increase retention of squalamine lactate in the targeted choroidal tissue, thus providing sustained anti-angiogenic concentrations in the posterior segment.

Q What biology would explain why the drug would work in classic CNV but not occult?
A Classic CNV lesions typically grow aggressively and may be well-suited for squalamine combination therapy, but this may not be the entire story. The IMPACT study data also demonstrated that lesions with smaller occult CNV components (<10 mm²), including occult-only lesions, had a similar benefit to what was seen in the classic CNV group, suggesting that the size of the occult component may play a bigger role in predicting the optimal patient population for treatment. Therefore, this treatment could be useful in both classic as well as occult-containing lesions.

Q Was the subgroup you describe as working pre-specified?
A The IMPACT study included treatment-naïve subjects with wet AMD: 142 patients with classic or occult-only CNV were enrolled, with a wide range of visual acuities and lesion sizes, and 128 completed the nine-month study. The key endpoints were number of p.r.n. ranibizumab injections, mean change in visual acuity, percentage of subjects with three-line visual acuity gain and safety. In a prespecified subgroup of patients with lesions containing classic CNV (squalamine n=37, Lucentis monotherapy n=28), mean gains in visual acuity at month nine were 11 letters in the squalamine combination arm vs. five letters in the Lucentis-only arm. The classic-containing CNV population represented approximately two-thirds of the total wet-AMD patient population.

Q What is the unmet need in the wet AMD space beyond the anti-angiogenesis and anti-permeability effects of existing anti-VEGF drugs?
A There is unmet need for treatments for patients who present later with more mature CNV. While anti-VEGF addresses endothelial cells, anti-PDGF may address pericytes in these more mature CNV lesions. Attacking these pericytes would potentiate anti-VEGF treatment. Anti-fibrosis and neuroprotection are other areas of unmet need.

REFERENCES
Optos has the only imaging technology that can capture ultra-widefield images of 200° or 82% of the retina. We have expanded our already extensive variety of imaging modalities with the addition of Indocyanine Green Angiography - optomap icg. See more, discover more, and treat more effectively.

Find out more about what’s new from Optos. www.optosnextgen.com
Is “better late than never” really the best approach for detecting CNV?

ForeseeHome can detect changes in metamorphopsia, often before the patient notices any visual symptoms, providing important early indications of the possible development of wet AMD. Detection of wet AMD when the patient is asymptomatic, with excellent visual acuity and small lesion size, provides the opportunity for the most effective treatment outcome.

ForeseeHome is available by prescription only.

Catch the progression of CNV at its earliest stage

ForeseeHome
AMD Monitoring Program

To learn more call 1-888-910-2020 or visit www.foreseehome.com

Indication for Use: ForeseeHome is intended for use in the detection and characterization of central and para-central metamorphopsia (visual distortion) in patients with age-related macular degeneration as an aid in monitoring progression of disease factors causing metamorphopsia including, but not limited to choroidal neovascularization (CNV). It is intended to be used at home for patients with stable fixation. ForeseeHome is not intended to diagnose; diagnosis is the responsibility of the prescribing eye-care professional.