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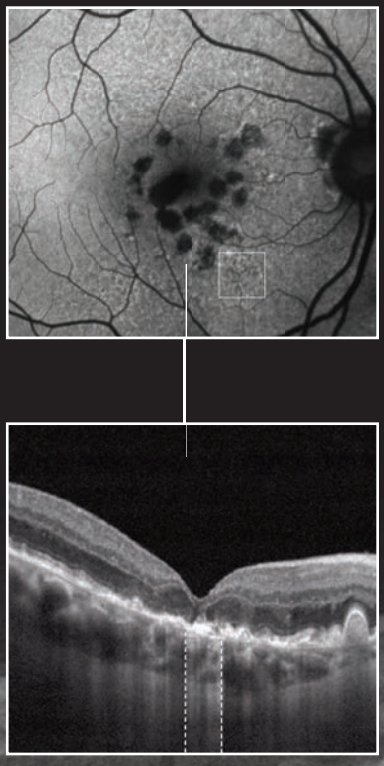
RETINA SPECIALIST

SEPTEMBER 2018



Focus on Imaging

HOW IMAGING CAN IDENTIFY PREDICTIVE BIOMARKERS OF AMD

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Evolving Role of Microperimetry PAGE 22

An Improved View Of Myopic Macular Degeneration PAGE 31

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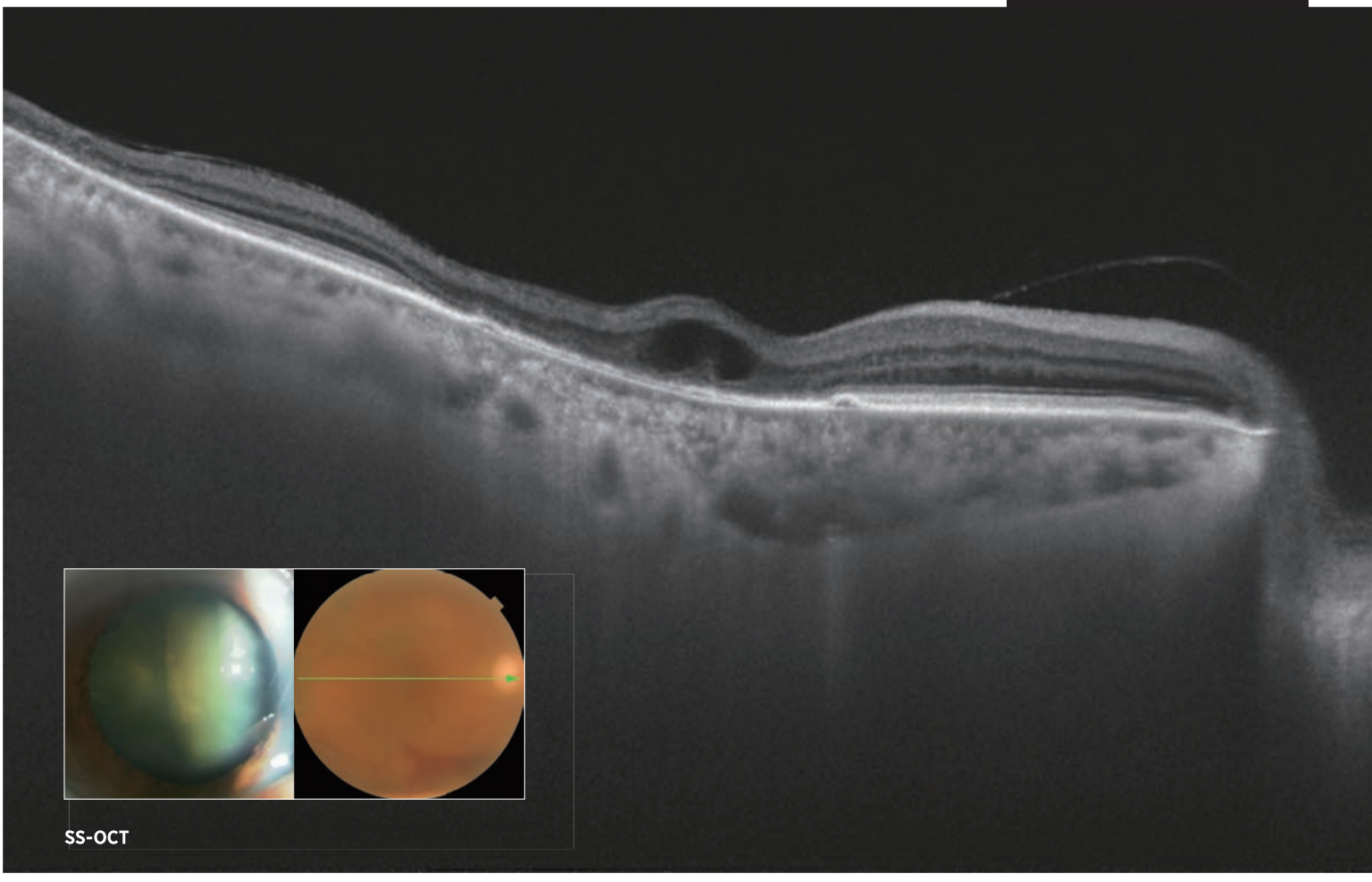

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EDITOR'S PAGE

By Charles C. Wykoff, MD, PhD

Show Me the Vision

As retina specialists, we rely heavily on both static and dynamic imaging platforms to inform diagnoses and guide our management decisions. Despite our dependence on imaging, however, most patients could not care less precisely what their imaging shows; they care about what they can see, and what they will be able to see moving forward.

Our imaging serves to provide us with biomarkers that allow indirect assessment of visual function. The National Institutes of Health defines a biomarker as, "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

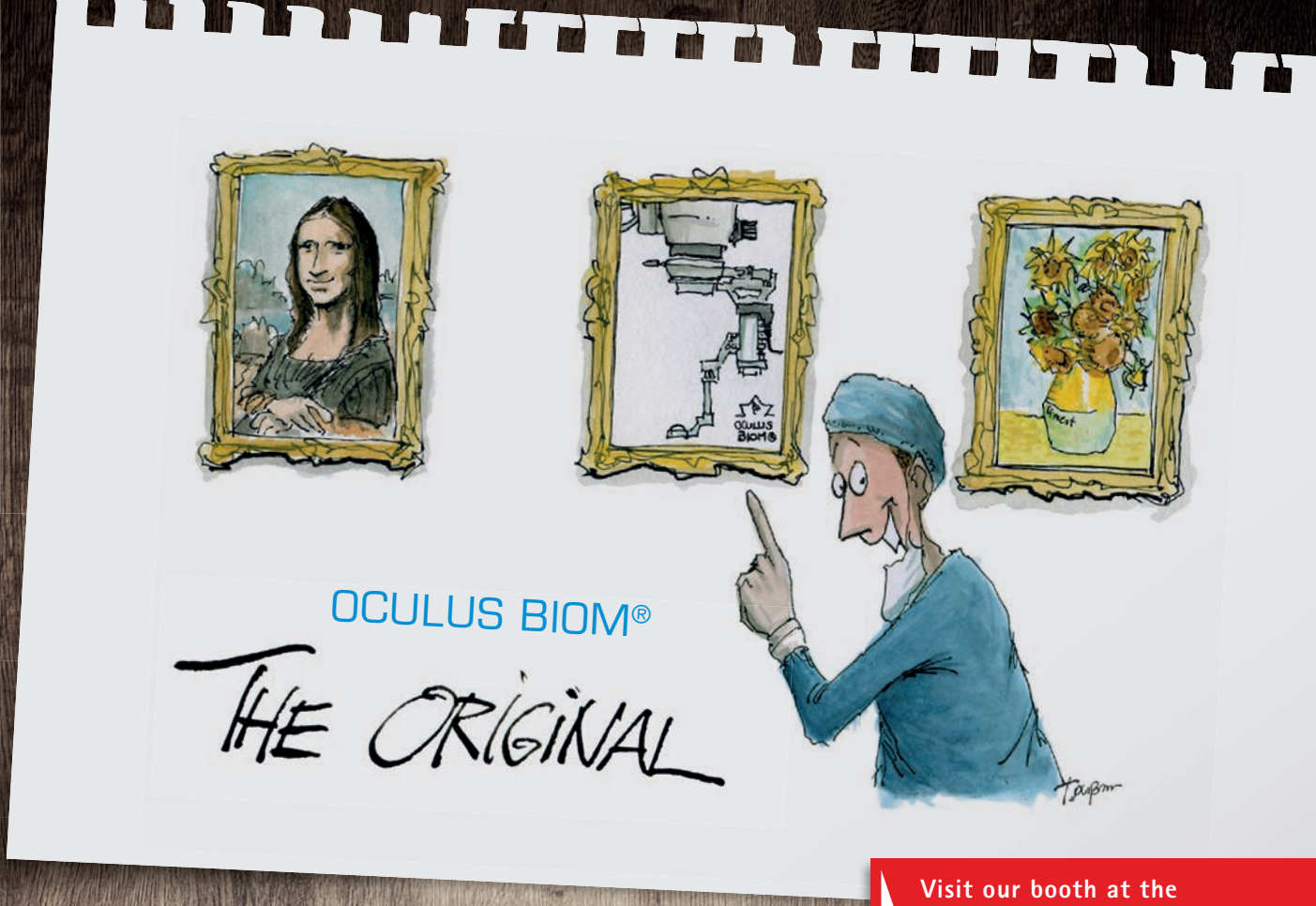
As our imaging capabilities advance, so does our knowledge of potential biomarkers. On page 16, Chris Or, MD, and Nadia Waheed, MD, MPH, describe more than a dozen biomarkers of age-related macular degeneration, based on optical coherence tomography and OCT-angiography, being investigated for their potential value in predicting disease progression to either geographic atrophy and/or neovascular AMD.

An appreciation of the prognostic significance of our imaging advances has defined entirely new categories of AMD, including nascent GA and non-exudative neovascular AMD. Such nomenclature expansion is impacting other disease states, too, including early stages of diabetic retinopathy harboring quantifiable pathology detectable with OCT-A, but not fundus photography.

Imaging characteristics hold substantial value if they can be reliably correlated with disease progression and/or functional endpoints. Traditionally, the Food and Drug Administration has used changes in central vision to guide approval of new pharmaceutical agents designed to treat vitreoretinal diseases. More recently, structural biomarkers have also been employed to seek drug approval, including change in DR severity using the Diabetic Retinopathy Severity Scale, release of vitreomacular traction by OCT and change in GA area by autofluorescence.

Moving forward, our field will certainly identify additional anatomic endpoints that can be correlated strongly enough with functional endpoints to be utilized as approvable endpoints. This is particularly needed in early disease states before significant central vision is lost, such as early diabetic macular edema. Developments in artificial intelligence, including deep-learning algorithms, appear capable of advancing prognostication towards the ultimate threshold of personalized medicine or, "an n of 1," as Anthony P. Adamis, MD, of Genentech recently eloquently predicted.

The philosophy of, "Show me the money," instilled in our culture by the 1996 movie "Jerry Maguire," seems particularly relevant. If we listen to our patients, and the FDA, they will tell us, sometimes more subtly than others, "Show me the vision."



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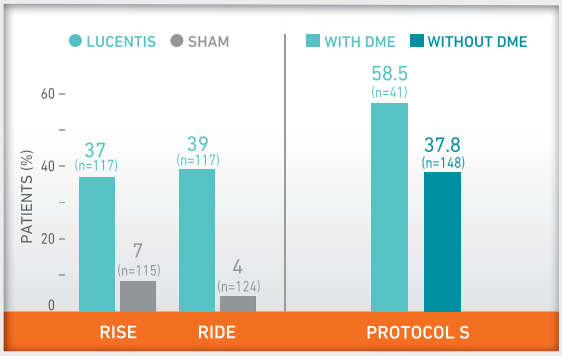
SIGNIFICANT REGRESSION IN DIABETIC RETINOPATHY

≥2-STEP IMPROVEMENTS AT 2 YEARS[1]*



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

RISE AND RIDE

- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S

- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).[1]

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:

- Diabetic retinopathy (DR)
- Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

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

*The following clinical trials were conducted for the **DR & DME** indications: *RISE & RIDE*—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. ***Protocol S***—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.[2,3]

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).[1]

VEGF, vascular endothelial growth factor.

0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED[1]

HELP PATIENTS TURN BACK TO AN EARLIER STAGE OF DIABETIC RETINOPATHY (DR)[1]

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a prefilled syringe. LUCENTIS is the only anti-VEGF approved for DR with or without diabetic macular edema (DME).[1]

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **2.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **3.** Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

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LUCENTIS®
RANIBIZUMAB INJECTION

LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

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

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

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

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

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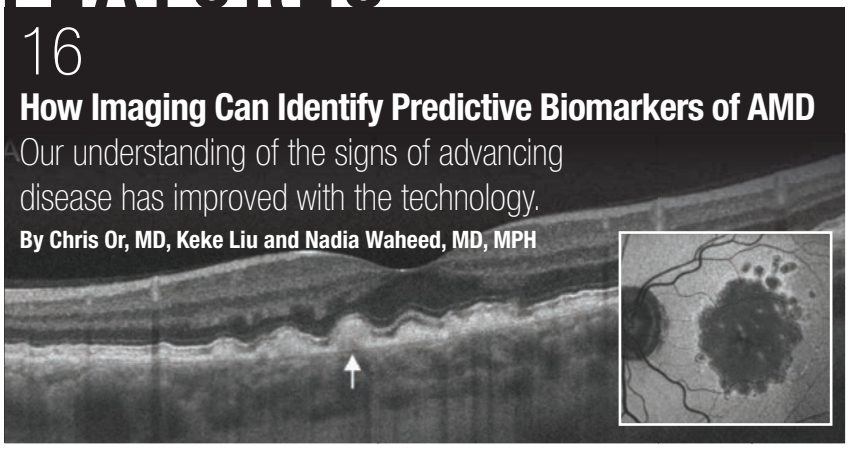
A PUBLICATION BY REVIEW

RETINA SPECIALIST

SEPTEMBER 2018

FEATURES



DEPARTMENTS

15,000 OCT Scans Contribute to an AI Platform That's 94 Percent Accurate

The race to develop artificial intelligence that can aid in the management of retinal diseases achieved a breakthrough last month when researchers from London's Moorfields Eye Hospital and Google DeepMind published a study that reported that their AI platform can recommend the correct referral decision for more than 50 eye diseases, with 94 percent accuracy.[1]

The researchers described how they successfully trained machine-learning technology using almost 15,000 optical coherence tomography scans to identify features of eye disease and recommend how patients should be referred for care.

"The number of eye scans we're performing is growing at a pace much faster than human experts are able to interpret them," says lead author Pearse Keane, MD, MSc, consultant ophthalmologist at Moorfields Eye Hospital National Health Service Foundation Trust, and National Institute for Health Research clinician scientist at the University College London Institute of Ophthalmology. "There is a risk that this may cause delays in the diagnosis and treatment of sight-threatening diseases, which can be devastating for patients."

Pearse Keane, MD, MSc, is leading the research collaboration with DeepMind at Moorfields Eye Hospital. (*Photo Courtesy Moorfields Eye Hospital*)

The AI technology Dr. Keane and his team are developing is designed to prioritize patients who need urgent treatment. "If we can diagnose and treat eye conditions early, it gives us the best chance of saving people's sight," he says. "With further research it could lead to greater consistency and quality of care for patients with eye problems in the future."

Using two types of neural networks, the AI system quickly learned to identify 10 features of eye disease from the OCT scans. The system was then able to recommend a referral decision based on the most urgent conditions detected. To validate that the AI system was making the correct referrals, clinicians also viewed the same OCT scans and made their own referral decisions. The study concluded that AI was able to make the right referral recommendation more than 94 percent of the time, matching the performance of expert clinicians.

IN BRIEF

Apellis Pharmaceuticals received fast-track designation from the Food and Drug Administration for APL-2, the company's novel complement factor C3 inhibitor for treatment geographic atrophy. Apellis plans to initiate a Phase III trial of patients with GA later this year.

Regeneron Pharmaceuticals received FDA approval of its supplemental Biologics License Application for Eylea (aflibercept) for a modified 12-week dosing schedule in patients with wet age-related macular degeneration.

The FDA granted **Wills Eye Hospital** approval to begin an early feasibility study to implant the **Alpha AMS** subretinal device (**Retina Implant**) in patients with blindness due to retinitis pigmentosa. The Alpha AMS has been designed to replace non-functioning and absent photoreceptor cells lost due to RP deterioration.

The DeepMind blog reported that the Moorfields clinicians capture more than 1,000 OCT scans a day, and the time that it takes to analyze them can lead to treatment delays.

The next step involves clinical trials of the technology.

Reference

1. De Faw J, Ledsam JR, Romera-Paredes B, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nature Med. 2018 August 13. [Epub ahead of print]

Study Finds Link Between Retinal Diseases and Alzheimer's

Researchers at the University of Washington have reported that patients with age-related macular degeneration and diabetic retinopathy, as well as glaucoma, may have an increased risk of Alzheimer's disease.[1]

The study involved 3,877 randomly selected patients from the Adult Changes in Thought Study, an ongoing prospective cohort study begun in 1994 that now includes more than 5,400 adults age 65 and older who were dementia-free at enrollment and followed until development of dementia, dropout or death. The study was published online in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*.

"We don't mean people with these eye conditions will get Alzheimer's disease," says lead researcher Cecilia Lee, MD, assistant professor of ophthalmology at the UW School of Medicine. "The main message from this study is that ophthalmologists should be more aware of the risks of developing dementia for people with these eye conditions, and primary care doctors seeing patients with these eye conditions might be more careful on checking on possible dementia or memory loss."

Over the five-year study, 792 cases of Alzheimer's disease were diagnosed among the cohort by a committee of dementia experts. Patients with AMD, DR or glaucoma were at 40 to 50 percent greater risk of developing Alzheimer's disease than similar subjects without these eye conditions. Cataract diagnosis was not an Alzheimer's disease risk factor.

"What we found was not subtle," says Paul Crane, MD, of UW School of Medicine. "This study solidifies that there are mechanistic things we can learn from the brain by looking at the eye."

The relationship between the eye and the brain requires more study, Dr. Lee says. Better understanding of neurodegeneration in the eye and the brain could bring more success in diagnosing Alzheimer's early and developing better treatments.

Funding for the research came from the National Institutes of Health, National Institute of Aging, National Eye Institute, an unrestricted grant from Research to Prevent Blindness, and royalties from UpToDate.

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What Did You Say I Have, Again?

An uncommon cause of unilateral macular edema, elucidated. ***By Ariel J. Tyring, MD***

A 68-year-old man presented to the University of Washington Eye Institute with complaints of progressively blurred vision and vertical visual distortion in the left eye for the last 10 years. His ocular history was significant for LASIK for myopia, and his medical history was notable for hyperlipidemia managed with an oral statin. His family history was negative for any eye diseases or blindness.

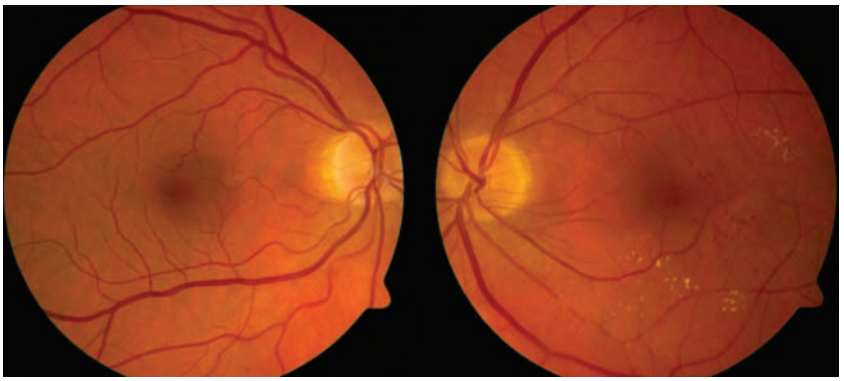


Figure 1. Fundus photographs show a few drusen in the nasal macula in the right eye and multiple dot blot hemorrhages with associated exudates and retinal edema in the temporal macula of the left eye.

Examination and Findings

Best-corrected visual acuity was 20/20 and 20/30 in the right and left eyes, respectively. Intraocular pressure was 10 mmHg in both eyes. Pupils were equal and symmetrically reactive without afferent pupillary defect. Extraocular motility and confrontational visual fields were full in each eye. Anterior segment exam was only notable for 1+ nuclear sclerotic cataracts in each eye.

Dilated fundus exam was unremarkable in the right eye apart from a few drusen in the nasal macula and inferior cobblestone degeneration. In the left eye, the dilated fundus exam demonstrated multiple dot blot hemorrhages with associated exudates and retinal edema in the temporal macula (*Figure 1*). Temporal and inferior lattice degeneration was visible in the periphery, as was a posterior vitreous detachment with a Weiss ring.

We noted some vascular dilatation in the left temporal macula, but no vascular tortuosity, cotton wool spots or peripheral hemorrhages in either eye.

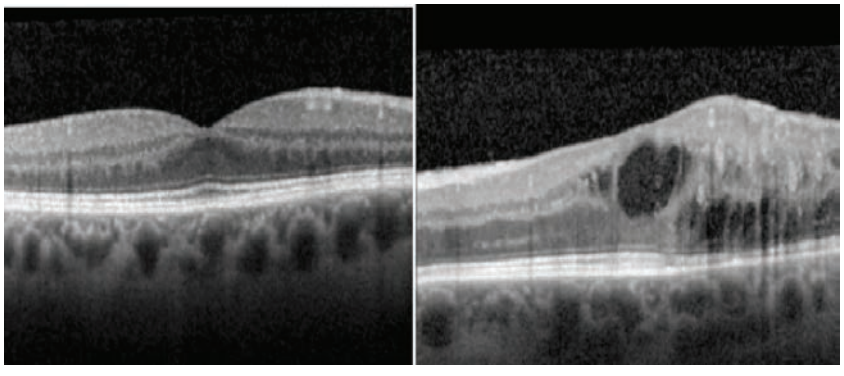


Figure 2. Optical coherence tomography shows normal foveal contour and retinal architecture in the right eye and retinal edema with intraretinal fluid and attenuation of the ellipsoid zone temporally in the left eye.

Workup

Optical coherence tomography showed normal foveal contour and retinal architecture in the right eye. OCT in the left eye showed loss of the foveal contour, intraretinal fluid centrally and temporally, attenuation of the ellipsoid zone temporally and dilated vascular walls (*Figure 2*).

Fluorescein angiography with transit of the left eye showed normal transit time and vascular filling, but demonstrated dilated, telangiectatic and aneurismal vessels temporal to the foveal center. Slow petalloid leakage around and temporal to the fovea in late frames was also noted. FA of the right eye showed a normal filling pattern without leakage or vascular abnormalities (*Figure 3*).

Diagnosis and Management

This patient had a mild reduction in visual acuity and visual distortion in the left eye with findings of unilateral retinal hemorrhages, telangiectasia, edema and aneurismal vascular dilatation in the temporal

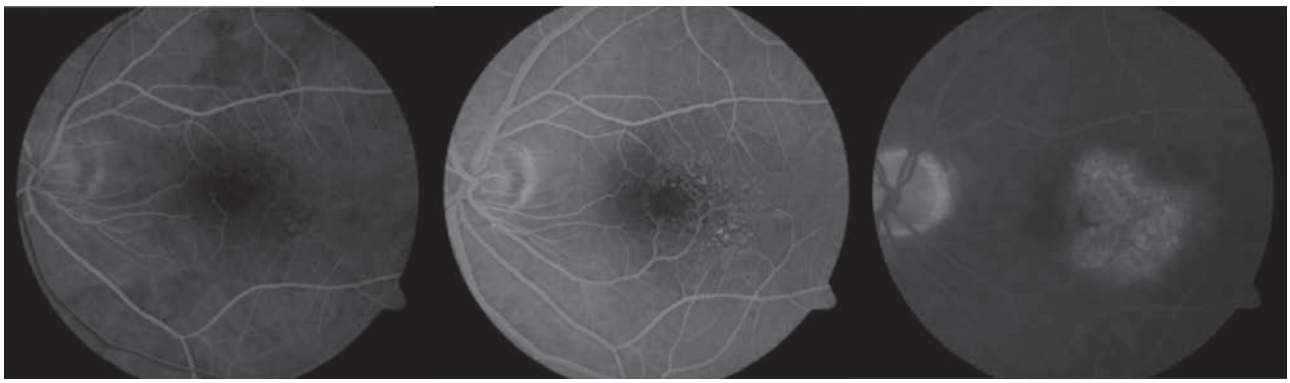


Figure 3. Fluorescein angiography with transit of the left eye shows dilated, telangiectatic and aneurismal vessels temporal to the foveal center with slow petalloid leakage around and temporal to the fovea in late frames.

macula. The differential diagnosis in this case of unilateral macular vasculopathy with telangiectasias and retinal edema should include retinal vein occlusion, diabetic retinopathy, radiation retinopathy, Eales' disease, idiopathic macular telangiectasia, Coats' disease and carotid artery obstruction.

This patient has no history of diabetes or radiation exposure. The normal transit time of the FA is not consistent with a diagnosis of ocular ischemic syndrome from carotid artery obstruction. The normal filling on FA without vascular tortuosity is not suggestive of retinal vein occlusion. Both Eales' and Coats' disease are characterized by unilateral aneurysmal telangiectasias with exudation, but the pathology is generally more widespread throughout the fundus and periphery in these cases. In contrast, the retinopathy in our case is confined to the parafoveal region, which led us to the diagnosis of Type 1 idiopathic macular telangiectasia.

We offered treatment for the macular edema with exudates, central IRF on OCT and active petalloid leakage on FA. Options reviewed included anti-VEGF therapy as well as laser photocoagulation. The patient elected for observation given his longstanding, stable and relatively mild symptoms, but he will consider treatment in the future.

Three Types of IMT

Idiopathic macular telangiectasia (IMT), also known as idiopathic parafoveal, perifoveal or juxtafoveal retinal telangiectasia, is a descriptive term used for a group of conditions characterized by exudation from ectatic and incompetent retinal capillaries in the juxtafoveal region.

This contrasts with conditions of generalized retinal telangiectasias, such as in Coats' disease, and with secondary retinal vascular abnormalities, such as those seen in vein occlusions, diabetes and carotid artery insufficiency. As the name suggests, the etiology of IMT is unknown.[1]

The condition was first classified in three broad groups by J. Donald Gass, MD, and Ray T. Oyakawa, MD, in 1982.[2] Group 1 IMT is characterized by unilateral parafoveal telangiectasias in the temporal macula, and is often accompanied by lipid-rich exudation. This is our patient's diagnosis, which we will mainly focus on.

Type 2 IMT is characterized by acquired bilateral telangiectasias, right-angled vessels, foveal atrophy, superficial crystals and, in some cases, choroidal neovascular membranes. Type 3 IMT, the rarest form, is characterized by progressive occlusion of the perifoveal capillary network.[1-3]

Idiopathic Macular Telangiectasia Type 1

Although IMT type 1 is considered congenital, it is nonfamilial. Males are most commonly affected and symptom onset usually occurs by age 35 years. FA typically shows prompt retinal vasculature filling and demonstrates the telangiectatic vessels of both the superficial and deep capillary networks in the temporal macula.

Because up to one-third of cases may have focal extramacular telangiectasias, many consider IMT to be within the spectrum of Coats' disease. Unlike Type 2 IMT, pigment proliferation and neovascularization is not characteristic of Type 1 IMT. Visual acuity is usually mildly affected, ranging from 20/25 to 20/40, with chronic cystoid macular edema as the most common cause of vision loss.[1-3]

(Continued on page 15)

By Paul Hahn, MD, PhD »

Managing Macular Folds After RD Repair

Sometimes re-detachment is the only solution. ***With Kyle Kovacs, MD and Anton Orlin, MD***

Macular folds are a rare but serious complication following retinal detachment surgery. They occur most often in bullous superior detachments with fluid extending to the fovea. When folds involve the fovea, patients can be profoundly symptomatic with visual loss, metamorphopsia or diplopia.

Prevention is Best Therapy

As with any complication, prevention is the best strategy. Surgical techniques during at-risk detachments should be modified to maximize drainage of subretinal fluid with use of perfluorocarbon liquid (PFCL) or with a posterior retinotomy. Thorough drainage prevents focal sequestration of fluid that might lead to fold formation once gas tamponade is introduced.

Immediately postoperatively, while still in the operating room, we position at-risk patients temporally for one hour prior to face-down positioning, as this column described previously.[1] This avoids the "downward sag" of the retina by gravity that ultimately drives fold formation.

The Case for Observation

Despite these efforts, macular folds may still occur. There are no clear recommendations regarding timing of surgery, and the natural history of folds can be highly variable. Some resolve without intervention (*Figure 1*).

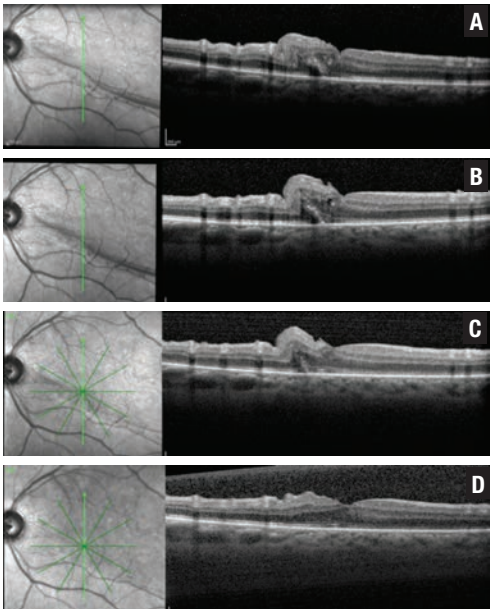


Figure 1. These scans illustrate a spontaneous fold resolution with postoperative observation. At one month (A) a macular fold is visible; visual acuity was 20/50. At two months (B), the vision and fold remained stable, with some anatomic improvement noted at four months (C). Vision improved to 20/40 with anatomic resolution of the fold at nine months (D).

Partial thickness folds (or "pseudofolds") are limited to either the inner or outer retina and can often be monitored for spontaneous resolution. Some authors have suggested that the presence of persistent subretinal fluid is a good prognostic indicator for spontaneous resolution. When we see relatively asymptomatic folds, partial thickness folds, subretinal fluid and/or folds demonstrating interval improvement, we continue to observe these cases every few weeks.

Operative Techniques

Symptomatic foveal folds (*Figure 2*) require timely surgical intervention to prevent photoreceptor damage and vision loss.

We focally detach the macula with balanced salt solution alone, incorporating the full extent of the fold with either a 38-gauge (MedOne) or 41-gauge (de Juan or de Juan/Awh, both Bausch + Lomb) subretinal cannula. We introduce the cannula

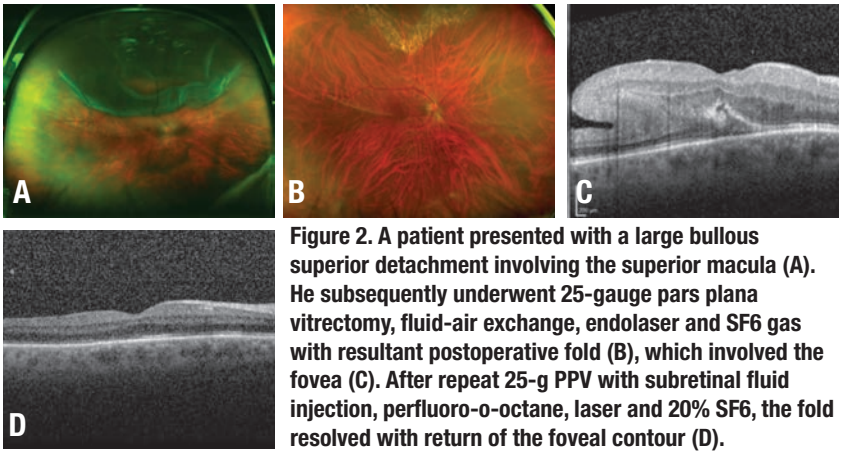
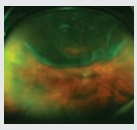


Figure 2. A patient presented with a large bullous superior detachment involving the superior macula (A). He subsequently underwent 25-gauge pars plana vitrectomy, fluid-air exchange, endolaser and SF6 gas with resultant postoperative fold (B), which involved the fovea (C). After repeat 25-g PPV with subretinal fluid injection, perfluoro-o-octane, laser and 20% SF6, the fold resolved with return of the foveal contour (D).

View the Video



Drs. Kovacs and Orlin demonstrate their technique for surgical management of macular folds. Available at: http://bit.ly/VideoPearl_007

into the subretinal space just within the macular arcade, away from the fovea and fold. This prevents a forceful stream of fluid directly to the fovea and minimizes fluid tracking peripherally through the fold. (Tip: a fluid-air exchange may be helpful if this occurs.)

We gently introduce saline to create a subretinal bleb that encompasses and stretches the entire macular portion of the fold. Additional bleb sites may be necessary to fully encompass the fold. A soft-tip cannula can be used to assess the memory of the fold to ensure that it is completely stretched over the bleb. Then we introduce PFCL to flatten the macula and displace the subretinal fluid to the periphery. A small, peripheral retinotomy is created to drain the subretinal fluid followed by fluid and PFCL-air exchange and endolaser to the peripheral retinotomy. We typically leave these eyes with a 20% SF6 bubble.

In the presented case, the patient was positioned face down due to superotemporal fluid displacement. If the excess fluid pushes to a different area of the retina, such as inferiorly or temporally, we position the patient accordingly, so that gravity continues to move the fold away from the fovea.

We hope to never see a fold, but these techniques should help us be equipped to manage this challenging complication if it arises.

Dr. Kovacs is a vitreoretinal fellow and Dr. Orlin is a vitreoretinal surgeon and assistant professor of ophthalmology at Weill Cornell Medical College, New York.

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What Did You Say I Have, Again?

(Continued from page 13)

Treatment of Type 1 IMT focuses on the management of CME. The mainstay of treatment has historically been photocoagulation, as Dr. Gass described.[2,4] Small (100 µm) burns of moderate intensity applied in a grid pattern to the temporal macula while avoiding the capillary-free zone have been found to be successful in reducing exudation and improving visual acuity.[2]

Intravitreal injection of triamcinolone acetonide has also been shown in case reports to reduce the volume of macular edema, but the effect was short-lived and visual acuity results were variable.[5]

More recently, intravitreal injection of anti-VEGF agents has been investigated. Early promising reports on the use of bevacizumab (Avastin, Roche/Genentech) demonstrated significant and sustained decrease in macular edema. However, others found that some Type 1 IMT patients may become refractory to bevacizumab and ranibizumab (Lucentis, Roche/Genentech).[6]

In one such case of a patient refractory to both intravitreal bevacizumab and laser photocoagulation, intravitreal aflibercept injection significantly improved both macular edema and visual acuity.[7]

Type 1 IMT is an uncommon condition characterized by unilateral telangiectasias in the temporal macula with exudation and macular edema contributing to mild degrees of visual impairment. The CME component of this disease can be managed with a combination of laser and anti-VEGF therapy, and the prognosis is favorable.

Quotable

Type 1 IMT is an uncommon condition characterized by unilateral telangiectasias in the temporal macula with exudation and macular edema contributing to mild degrees of visual impairment.

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Dr. Olmos de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington in Seattle, where Dr. Tyring is a first-year fellow in vitreoretinal surgery.

Focus on Imaging

HOW IMAGING CAN IDENTIFY PREDICTIVE BIOMARKERS OF AMD

Our understanding of the signs of advancing disease has improved with the technology to identify them.

By Chris Or, MD, Keke Liu and Nadia Waheed, MD, MPH

The five-year risk of progression from intermediate age-related macular degeneration to advanced disease has been known to range from 0.5 percent to 50 percent, depending on disease severity,[1] and researchers have long pursued identification of biomarkers that could be predictive of the risk of advancing disease.

Many studies have attempted to identify predictive biomarkers for the progression of intermediate AMD to advanced AMD. Among the risk factors natural history studies have demonstrated for progression to advanced AMD are advanced AMD in the fellow eye, large, soft drusen and AMD-related pigmentary abnormalities (*Figure 1*).[1]

Because of this, biomarkers on imaging studies, most notably on optical coherence tomography, have become an attractive option due to the ease of acquisition and ubiquity of OCT. In particular, various authors have described drusen characteristics as risk factors for the progression of AMD.[2,3]

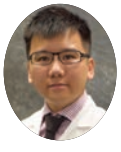
Available OCT algorithms can aid in following drusen load, described by the height, area and volume of drusen over time, and can identify biomarkers for progression to advanced AMD.[2] This article will review the evidence supporting the use of OCT and fundus autofluorescence to identify biomarkers of advancing AMD.

AMD Classifications

The Age Related Eye Disease Study (AREDS) group classifies AMD into three categories, based on the type and severity of fundus lesions, including drusen dimensions and pigmentary changes that have been demonstrated to be of value in predicting the risk of AMD progression:[1]

- early AMD, defined as the presence of medium drusen (63 to 125 µm) with no pigmentary abnormalities;
- intermediate AMD, defined as the presence of large drusen (>125 µm) or medium drusen in the presence of pigmentary abnormalities; and
- advanced AMD, characterized by neovascularization and/or geographic atrophy.[4]

ABOUT THE AUTHORS



Dr. Or is a research fellow at New England Eye Center, Tufts University School of Medicine, Boston, and currently a first-year ophthalmology resident at Louisiana State University-New Orleans.

Dr. Waheed is associate professor of ophthalmology at Tufts University School of Medicine and consultant to its affiliated New England Eye Center, and director of the Boston Image Reading Center.

Mr. Liu is a second-year medical student at the University of Hawaii John A. Burns School of Medicine.

Disclosures: Dr. Waheed disclosed financial support from the Macula Vision Research Foundation, Topcon Medical Systems, Nidek Medical Products, Optovue (consultant) and Carl Zeiss Meditec.

Drusen Characteristics

Both drusen area and volume have been associated with the development of GA and neovascular AMD, based on findings from researchers at the University of British Columbia, who studied 83 patients with intermediate AMD.[2] This may result from focal loss of the overlying photoreceptors and the outer retina due to focal disruption and compression. Others have suggested drusen height may be a risk factor for intermediate AMD progression.[5,6]

A small study of 30 patients reported that a subgroup that progressed to neovascular AMD had a mean drusen height of 122 µm, whereas the group that did not progress had a mean drusen height of 71 µm.[6] A larger study at Stanford University described a statistical model using spectral-domain OCT scans of patients with early and intermediate AMD and reported that drusen area, volume and height predicted progression to advanced AMD.[5]

Analyzing 143 eyes with nonexudative AMD, researchers at Bascom Palmer Eye Institute reported that in 12 percent of cases, drusen volume actually decreased with a magnitude dependent on the baseline drusen volume.[7] The AREDS group reported that drusen regression is a risk factor, as 82 percent of the eyes that developed GA had preceding drusen regression and hypopigmentary changes.[8] Austrian researchers further supported this finding; in 50 eyes with early to intermediate AMD, drusen regression occurred in 44 percent of the cohort, which preceded the progression to advanced AMD—both GA and nAMD—in every case in their study.[3]

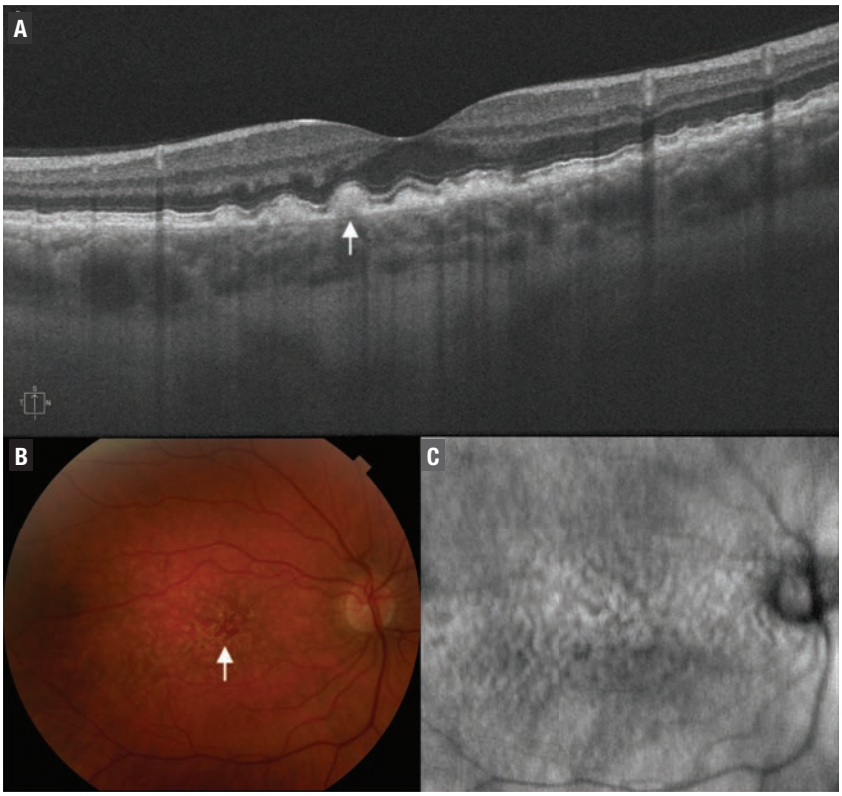


Figure 1. B-scan optical coherence tomography demonstrates large soft drusen (A), depicted as retinal pigment epithelium elevations greater than 125 µm (arrow). Also shown are the corresponding color fundus photograph (B) and en-face OCT image (C).

Other Predictive Lesions

Other signs described as precursor lesions for the development of advanced AMD include hyper-reflective foci, reticular pseudodrusen, nascent GA, subretinal pigment epithelium reflective columns and OCT-reflective drusen substructures.[9]

• ***Hyper-reflective foci.*** Authors have described hyper-reflective foci as representing pigment migration, displacement and clumping of degenerated retinal pigment epithelium cells. An extension of the AREDS2 study using SD-OCT demonstrated that patients with hyper-reflective foci on OCT at baseline had a fivefold increased risk of progression to GA, but not wet AMD, at two years when compared with controls.[9]

• ***Reticular pseudodrusen.*** These subretinal collections of granular, hyper-reflective material are found most commonly in the superior macula or superotemporal arcades (*Figure 2, page 18*). Reticular pseudodrusen are

Take-home Point

Researchers and clinicians have pursued identifying biomarkers that can be predictive of a patient's risk of advancing from intermediate to advanced age-related macular degeneration. Optical coherence tomography, especially OCT angiography, has emerged as a useful tool to identify those biomarkers, as has fundus autofluorescence. This article reviews markers of advancing disease and how imaging aids in identifying them.

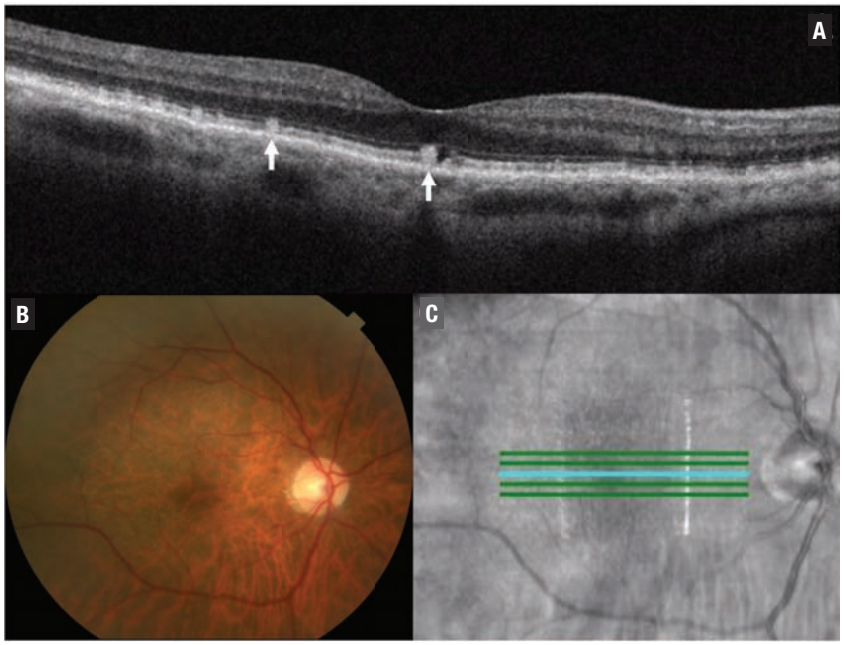


Figure 2. Optical coherence tomography of the macula shows the presence of reticular pseudodrusen (A), which are subretinal collections of granular and hyper-reflective material (arrow). Also shown are the corresponding color fundus photograph (B) and en-face OCT image (C).

found to be present in approximately 9 to 58 percent of patients with intermediate AMD, depending on the population studied.[10,11] Researchers in Australia reported that the presence of reticular pseudodrusen is associated with an additional 2.64-fold increased risk of progression to nAMD or central GA, with the risk of progression higher for reticular pseudodrusen located outside the macula.[10]

• ***Nascent GA.*** A term that Zhichao Wu, PhD, and colleagues first described, nascent GA was found in 22 percent of eyes with intermediate AMD (*Figure 3*).[12] Characterized by the loss of the outer retina without definite RPE loss, nascent GA is typically located within the central macula; its location corresponds to the location predisposition of GA.[12,13] An average of 11 months elapsed between early signs of nascent GA and the development of GA,[12] but an association with wet AMD has not been reported.[13] Nascent GA was recently renamed iRORA (incomplete retinal pigment epithelium and outer retinal atrophy) by the Classification of Atrophy Meetings study group.[14]

• ***Sub-RPE hyper-reflective columns.*** These narrow columns of hyper-reflectivity seen under the RPE suggest deficiencies in the RPE layer.[15] Lissa Padnick-Silver, PhD, and colleagues described sub-RPE hyper-reflective columns in 27 percent of eyes that progressed to nAMD in their cohort, which preceded the onset of exudative changes or GA by at least three months.[15]

• ***OCT-reflective drusen substructures.*** Variation in the structure and properties of drusen as they appear on OCT has also been proposed to portend an increased risk of AMD progression. On OCT, drusen usually appear as a smooth, dome-shaped RPE elevation with homogeneous medium internal reflectivity. However, varying morphology, reflectivity and internal homogeneity may be observed.

A large multicenter study investigated such variations in 349 patients

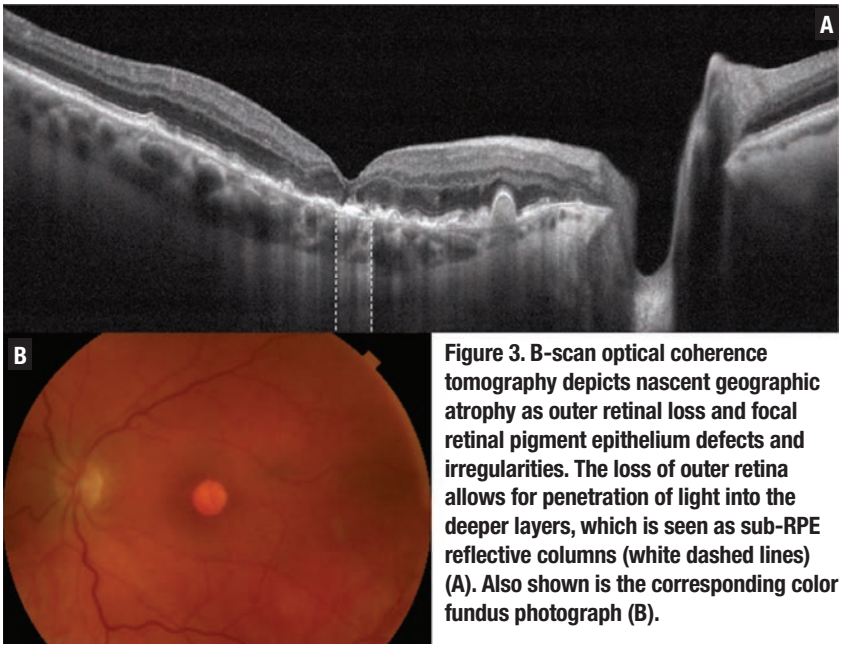


Figure 3. B-scan optical coherence tomography depicts nascent geographic atrophy as outer retinal loss and focal retinal pigment epithelium defects and irregularities. The loss of outer retina allows for penetration of light into the deeper layers, which is seen as sub-RPE reflective columns (white dashed lines) (A). Also shown is the corresponding color fundus photograph (B).

with intermediate AMD enrolled in the AREDS2 SD-OCT study.[16] The authors described four phenotypic subtypes of variations or OCT-reflective drusen substructures (ODS):

- low-reflective cores;
- high-reflective cores;
- conical debris; and
- split drusen.

Presence of ODS at baseline was associated with progression to GA, but not to CNV, in eyes with intermediate AMD.[16]

• ***Other morphologic features.*** Other morphologic features found on OCT have been associated with AMD progression. Ellipsoid zone disruption has been associated with progression to advanced AMD and neovascularization, with an odds ratio of 17.9.[13]

Other features also independently associated with progression to advanced AMD, based on a multivariate stepwise model, include presence of drusenoid RPE detachment, presence of RPE thickening, focal irregularity (thickening or thinning) of the retina, irregularity or disruption of the external limiting membrane and choroidal vessel abnormalities noted on OCT.[13] Similarly, researchers in South Korea have described subfoveal choroidal thickness as a possible marker for GA progression.[17]

Emergence of OCT-A

The recent advent of OCT angiography provides a rapid and noninvasive method by which clinicians and researchers can diagnose and monitor nonexudative neovascularization in eyes with dry AMD.[18] A multicenter study and a French study were among the first to demonstrate the ability of OCT-A to detect nonexudative neovascularization in patients with phenotypic dry AMD.[19,20] These authors reported that the lesions demonstrated ill-defined hyperfluorescence with no leakage on fluorescein angiography, hypercyanescence in a plaque configuration on indocyanine green angiography, and a shallow, irregular pigment epithelial detachment with moderate hyperreflectivity and a major axis in the horizontal plane.

A follow-up study using swept-source OCT-A reported that 14.4 percent of patients with intermediate and late nonexudative AMD, who had exudative AMD in the fellow eye, had evidence of subclinical macular neovascularization (MNV).[21] Patients with phenotypic intermediate dry AMD, but who had subclinical MNV, carried an increased risk of conversion to exudative AMD compared to patients who did not have nonexudative MNV (21.1 percent vs. 5.4 percent at one-year follow-up).

Swept-source OCT-A, with its longer wavelength and deeper tissue penetration, has also been used to image the choriocapillaris in patients with intermediate and advanced AMD. A multinational study demonstrated focal choriocapillaris flow impairment associated with areas of nascent GA and drusen-associated GA.[22] Other authors have postulated that choriocapillaris flow is impaired under drusen, which may represent a promising clinical marker for disease progression.[23]

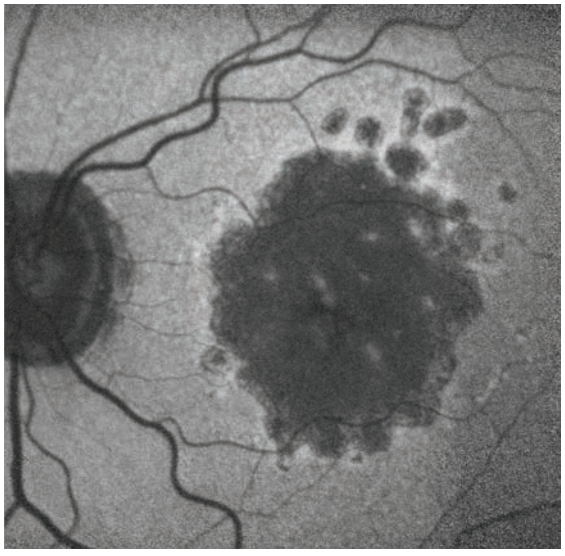


Figure 4. Fundus autofluorescence image of geographic atrophy exhibits a banded pattern surrounding areas of atrophy, which carries an increased risk of age-related macular degeneration progression.

FAF in AMD

Investigators have described the use of other imaging modalities, such as fundus autofluorescence (FAF), in intermediate AMD. Although varying patterns of FAF have been described, no particular pattern has been associated with conversion or progression of intermediate AMD.[24] However, researchers in Portugal reported that FAF abnormalities were predictive of progression to advanced AMD, with a 93 percent sensitivity.[24]

Hyperfluorescence surrounding GA has also been noted on FAF, with certain junctional patterns associated with an increased risk of GA progression. The Fundus Autofluorescence in Age-related Macular Degeneration (FAM) study characterized abnormalities in the junctional zone of GA into four categories:[25]

- focal increased;
- banded;
- patchy; and
- diffuse.[26]

Progression rates in eyes with the banded and diffuse FAF pattern were significantly higher compared to eyes without FAF abnormalities or with focal FAF patterns (*Figure 4*). An additional diffuse trickling pattern exhibited an even greater progres-

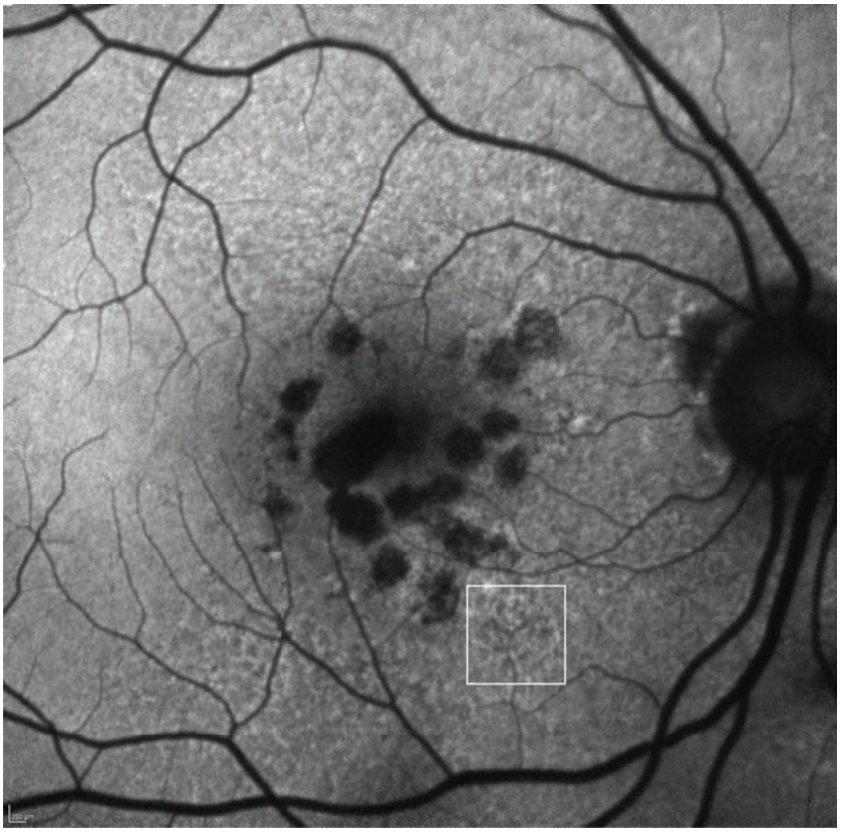


Figure 5. Fundus autofluorescence of multifocal geographic atrophy presenting as multiple discrete foci of retinal pigment epithelium atrophy, which carries a risk of geographic atrophy progression. Reticular pseudodrusen is also visible (white square).

sion of GA when compared to the other diffuse types.[26] Furthermore, the presence of multifocal atrophic spots and extrafoveal lesions were biomarkers predictive of GA progression (*Figure 5*).[27]

Because AMD progression carries a significant negative visual prognosis, its detection has crucial clinical implications. Not only do predictive biomarkers seen on imaging provide insight into AMD progression; they may also prove valuable in managing and monitoring this disease.

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Focus on Imaging

THE EVOLVING ROLE OF MICROPERIMETRY

What we know about MP, how it differs from traditional perimetry and why we should use it.

Linda Huang, Alec Fields, Bright S. Ashimatey, PhD, and Amir H. Kashani, MD, PhD

Traditional perimetry is a form of visual-function testing that has been used most commonly in glaucoma to evaluate changes in visual function when visual acuity is not the best indicator of disease progression,[1] This limitation also applies to many retinal diseases in that traditional visual acuity does not reflect the severity or onset of the disease process.

In retinal degeneration, functional findings from visual field (VF) measures can often be used to complement visual-acuity testing for diagnosis and assessment of its progression. For example, subjects with neovascular or non-neovascular advanced age-related macular degeneration can still have excellent visual acuity but complain of metamorphopsia and decreased quality of vision in the central 10 to 20 degrees. So why not use Humphrey visual fields to evaluate patients with retinal diseases?

Unfortunately, traditional VF testing is not useful in most patients with retinal disease because central fixation is often impacted and VF tests are too unreliable. In fact, even microsaccades and drifts in relatively normal subjects significantly impact the reliability of traditional visual fields, and the learning curve for reliable performance on VF is well demonstrated.[2] In addition, there is a need to correlate visual function with the clinical appearance of retinal pathology that is not possible with traditional VF, but is essential in retinal disease assessment.

How MP Addresses Limitations of Visual Fields

MP addresses both major limitations of traditional VF assessments as they pertain to retinal diseases. Namely, MP uses real-time tracking of the retinal movements during testing to provide spatially registered measurements of retinal sensitivity on a fundus image of the retina by (*Figure 1*). This minimizes the impact of poor fixation and also provides a fundus image registered

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to the retinal sensitivity measurements for the clinician to review.

Retinal tracking is commonly performed with a scanning laser ophthalmoscope (SLO) that detects movement of the retina in real time and allows the device to correct the position of the light stimulus for any changes in fixation. This helps to reduce errors that eye movements cause on the retinal locations the test stimulates, and allows for an improved test-retest of the same retinal location.[3] This correction is particularly useful in assessing residual visual function for patients who have severe vision loss and/or eccentric fixation.[3] One additional benefit of this tracking feature is that MP devices can provide information on fixation patterns and preferred retinal loci.

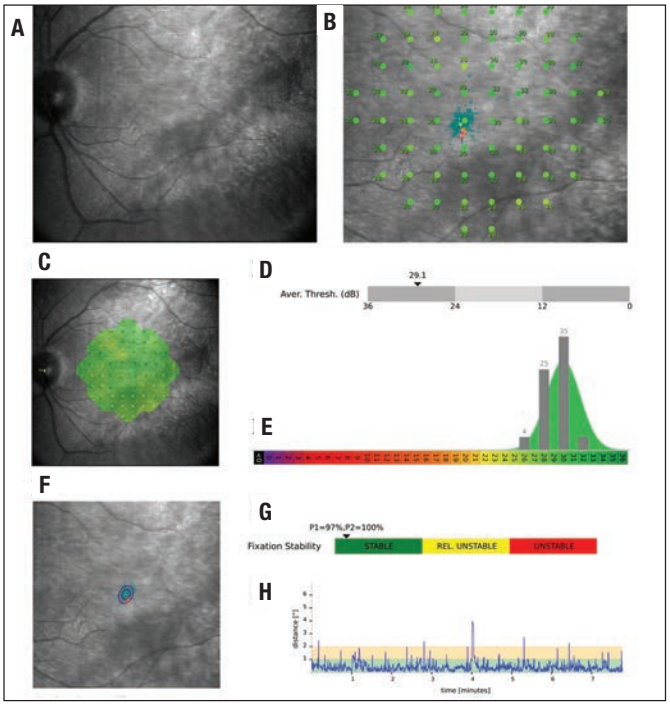

Figure 1. Example of microperimetry results in a healthy subject: A) scanning-laser ophthalmoscope (SLO) image of the fundus; B) retinal sensitivity measures superimposed on the SLO fundus image; C) retinal-sensitivity measures interpolated in a retinal-sensitivity map; D) average sensitivity threshold (dB; arrow indicates average sensitivity measure); E) distribution of sensitivity thresholds shown in bars, superimposed on a normative database (hotter colors indicate further deviations from the normative database); F) fixation points (blue dots) superimposed on SLO fundus image (fixation stability is computed using the bivariate contour ellipse area analysis); G) classification of fixation stability; and H) fixation stability plotted at individual time points.

Available Devices

Currently, three commercially available microperimeters are available: the Nidek MP-3 (Nidek Technologies); the Optos OCT/SLO (Optos) and the MAIA microperimeter (MAIA). Except for the added optical coherence tomography component of the Optos OCT/SLO, these devices have similar functions but differ in their dynamic range. For example, the dynamic range of the MP-3, Optos OCT/SLO and MAIA are 0 to 34 dB, 0 to 20 dB and 0 to 36 dB, respectively.[3-5]

In addition, the background luminance, maximum stimulus luminance and stimuli projection system of the devices differ. In a recent report comparing the findings from Nidek MP-3 and MAIA in healthy subjects, retinal sensitivity measures were higher with MAIA than with the MP-3.[6] These relationships were consistent between the devices and application of a 5.65-dB correction factor was able to interrelate the measurement from the two instruments.[6]

Utility of Fixation Testing

In addition to retinal sensitivity, MP devices also document the stability of fixation by measuring the subject's fixation location up to 25 times per second. Fixation testing refers to measuring the precision of the eye fixating on a target for a certain period of time, and has been demonstrated to be relatively stable in normal subjects regardless of age.[7,8]

Fixation stability in general is significantly associated with visual acuity[7,9] and is reduced in eyes with macular disease, but it may explain how a subject with severe disease is maintaining relatively good vision.[10] During the fixation test, retinal

Take-home Point

Microperimetry (MP) has emerged as a useful clinical tool to evaluate macular dysfunction, but retina specialists have a limited understanding of how this technology works and how they can use it in clinical or research settings. While visual acuity is the most widely used functional test in clinical practice, it alone is not a sensitive indicator of visual function in retinal degenerative diseases. MP is unique in its ability to combine fundus imaging with visual-field testing, and it possesses many other features that enhance its utility in the clinic. This review explains what MP is, how it differs from traditional perimetry measurements, and how it is being used in both clinical practice and clinical trial settings.

landmarks are tracked and subsequently plotted as a cloud of fixation points over a fundus image, revealing what portion of the retina the subject was using to see the stimulus. The resulting scatter plot can then be mathematically analyzed to assess fixation stability (*Figure 1, page 23*).

Fixation stability can be reported using one of two general approaches. For example, a simple clinical classification proposed by Gildo Fujii, MD, and colleagues[11] calculated the percentage of fixation points falling within a circle of 2 or 4 degrees in diameter and classifies fixation into one of three categories:

- stable—more than 75 percent of fixation points fall within a 2-degree circle;
- relatively unstable—fewer than 75 percent of fixation points fall within a 2-degree circle but more than 75 percent of fixation points fall within a 4-degree circle; and
- unstable—fewer than 75 percent of fixation points fall within a 4-degree circle.[11]

The percentage-based fixation stability measure is advantageous because of its clinical thresholds, but the 75 percent threshold has been criticized as too low. A recent study revealed that eyes with intermediate AMD were considered "stable" because of the low threshold.[15] Furthermore, healthy individuals typically have more than 97 percent of their fixation points within the 4-degree circle.[11,15]

Bivariate Contour Ellipse Area

In contrast, another method uses bivariate contour ellipse area (BCEA), as Michael Crossland, PhD, and colleagues have suggested.[10] The BCEA method calculates the area and orientation of an ellipse encompassing a given proportion of the fixation points' dataset, where lower BCEA values indicate better fixation stability. Different authors have used three different statistical thresholds—63 percent,[8,12] 68 percent[13] or 95 percent[14]—to calculate BCEA, but no clear evidence suggests which is the best.

BCEA is useful because it is a mathematical model capable of describing irregularly shaped sets of points, but it does not have widely accepted cutoffs to distinguish between stable and unstable fixation. Also, it's not clear that the distribution of fixation points is normally distributed, which is the assumption of the BCEA model.

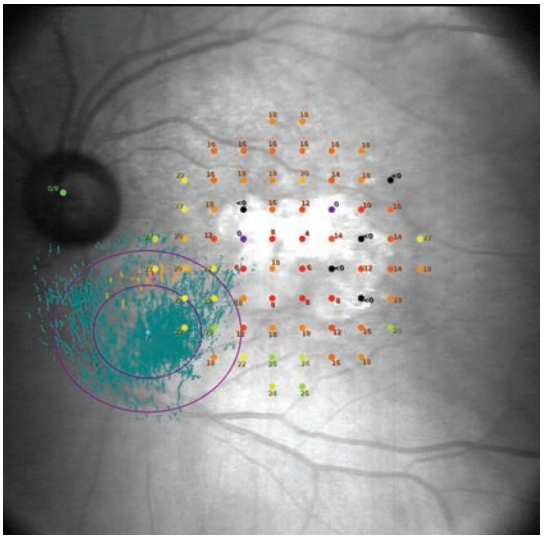

Figure 2. Preferred retinal locus (PRL) and fixation stability in a subject with non-neovascular age-related macular degeneration and geographic atrophy. The two purple ellipses show the bivariate contour ellipse areas encompassing 63 percent and 95 percent of the fixation points, respectively. The center of the ellipse shows the PRL. Fixation stability in this subject was graded as unstable.

Individuals with macular disease compensate for the loss of central vision by using healthy parts of the retina called preferred retinal loci (PRL).[7] PRLs can develop on any part of the retina. They can be single or multiple, and can offer superior vision compared to other retinal areas.[7,15]

Microperimeters offer the ability to accurately determine the precise location of a PRL, indicated as a circumscribed area with a majority of fixation points as determined by one of the methods described previously or by qualitative inspection (*Figures 1 [page 23] and 2*).[15] The distance from the estimated anatomical fovea, the pattern, the orientation and number of PRL can be calculated and also be used as a measure of visual function.[15]

The unique ability of MP devices to measure fixation and retinal sensitivity in a spatially registered manner with fundus images has enabled MP to become an increasingly useful method of detecting subclinical changes in early states of disease as well as very advanced disease.

MP in AMD

MP has a high test-retest reliability in patients with early and intermediate stages of macular disease.[16] In one study, 200 healthy controls demonstrated the highest mean retinal sensitivity, whereas among the 200 individuals with AMD the mean sensitivity for those with early AMD was higher than for those with intermediate AMD.[17] In a study identifying visual-function metrics to evaluate stages of AMD, standard and computerized low-luminance visual acuity, MP, cone contrast testing and dark adaptation all distinguished

early from intermediate AMD.[18] Of these measures, however, the thresholds for MP average and percent-reduced were found to be the most sensitive measures to distinguish between all groups.[18] Thus, MP is a more sensitive indicator of disease severity compared to other functional measures.

Individuals with advanced macular degeneration have impaired retinal sensitivity and fixation stability, contributing to poor visual performance (*Figure 2*). Fixation stability was shown to deteriorate from stable to unstable in eyes with intermediate AMD over a six-year period.[19] Positive correlations were found between fixation stability, visual acuity, PRL distance from the former fovea, and time since diagnosis, suggesting that the PRL becomes wider and farther from the former fovea as time progresses.[7] By tracking fixation stability and location of PRLs, MP can provide a comprehensive assessment of macular function and monitor natural disease progression.

MP has also been used to examine the relationship between visual function and retinal morphology using spectral-domain OCT. Patients with early AMD have shown significant thinning of the outer segment (OS) layer, and thickening and elevation of the retinal pigment epithelium in areas with VF defects compared to locations without defects.[20] RPE-plus-OS volume was also positively correlated with retinal sensitivity, indicating that a thicker outer retina was associated with better sensitivity.[21]

In eyes with geographic atrophy, the average retinal sensitivity of areas with photoreceptor damage outside the area of RPE loss was lower than that of the area without such photoreceptor damage; and this area of damage was larger in eyes with pseudodrusen.[22] Retinal sensitivity appears to drop precipitously at the margins of GA lesions compared to eyes with less advanced non-neovascular AMD.[23] Partial outer retinal thickness, defined as the distance between the outer plexiform layer and the ellipsoid zone, and retinal sensitivity were decreased over areas with retinal drusen compared to unaffected retinal areas.[24] By correlating areas of visual defects to structural abnormalities, MP allows for topographic evaluation of macular disease to reveal associations that were otherwise not known.

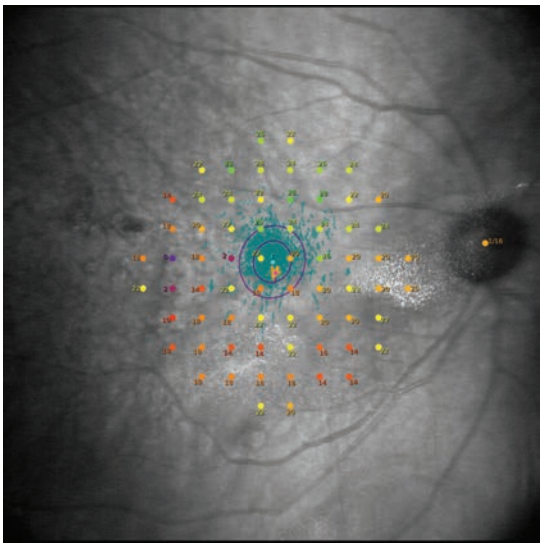

Figure 3. Retinal sensitivity findings in a patient with nonproliferative diabetic retinopathy. Retinal sensitivity is generally decreased over areas with hard exudates. Green indicates a region with greatest sensitivity (normal sensitivity) and red indicates a region with lowest sensitivity.

Changes in retinal sensitivity and fixation stability measured by MP have also been used as outcome measures in medical or surgical interventions for AMD. In individuals with wet AMD undergoing anti-VEGF therapy with bevacizumab (Avastin, Roche/Genentech), mean sensitivity increased as retinal thickness decreased, and decreased as retinal thickness increased after six months of intravitreal injections.[25] In a clinical trial assessing the safety and efficacy of a human embryonic stem-cell-derived RPE implant in five subjects with advanced non-neovascular AMD, two eyes improved from unstable to stable fixation after implantation.[27]

MP in Diabetic Retinopathy

MP has been used to investigate the occurrence of neuronal damage before clinical evidence of diabetic retinopathy.[28] Studies have shown that retinal sensitivity decreases in eyes with DR, and this was significantly lower over areas with hard exudates (*Figure 3*).[29] Glucose control also affects retinal sensitivity, with HbA1c values accounting for a 54.5-percent reduction in retinal sensitivity.[30] In a study comparing diabetic subjects with and without retinopathy, statistically significant differences were reported in foveal thickness, photoreceptor layer thickness, and mean RS.[31]

In a large population-based study of 357 subjects with diabetes, a reduction in mean retinal sensitivity was significantly correlated to central foveal thickness in subjects with no DR, suggesting early neuronal degeneration in diabetic retinopathy.[32] Another study further explored this structure-function relationship, showing a significant correlation between retinal sensitivity and ganglion cell layer-inner plexiform layer

(GCL-IPL) thickness in subjects with diabetes, but not in healthy controls.[33] No significant differences in best-corrected visual acuity were found between the two groups, indicating that neuronal damage may be present in individuals who may otherwise appear normal by conventional visual-acuity measures.[33]

Retinal sensitivity measured by MP has also been used as an important functional metric in the evaluation of diabetic macular edema. A significant inverse relationship was found between retinal sensitivity and normalized macular thickness in patients with clinically significant macular edema, with a decay of 0.83 dB for every 10-percent deviation of retinal thickness from normal values.[34] However, another study found no significant correlation between retinal sensitivity and retinal thickness in focal DME, but did find a significant reduction in retinal sensitivity and increase in retinal thickness for eyes with edema secondary to branch retinal vein occlusion.

Greater retinal sensitivity also correlated with faster maximum reading speed (MRS) and better BCVA in DME patients.[35] While MRS is not a practical measure of retinal function because it can be inconsistent and is affected by language barriers and educational level, MP testing is a fast and effective marker of retinal function.

Fixation characteristics have also been described in the evaluation of diabetes. Visual acuity is significantly reduced in diabetic patients with relatively unstable and poor central fixation.[36] In a study of patients with DME, fixation location and stability were not significantly influenced by edema characteristics, except for the presence of subfoveal hard exudates.[37] Patients with DME who underwent monthly intravitreal ranibizumab injections (Lucentis, Roche/Genentech) demonstrated a significant reduction of central retinal thickness, increased BCVA, and improved fixation stability over a three-month period.[38]

MP in Stargardt's

In patients with *ABCA4*-associated Stargardt's disease (STGD), MP has been used as an outcome measure for monitoring disease progression (*Figure 4*). Macular sensitivity has been used to quantify the decline of visual function in longitudinal studies of patients with STGD.[39]

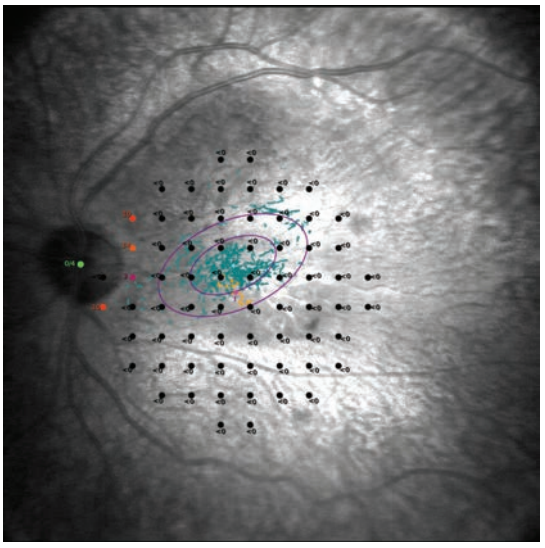

Figure 4. Microperimetry findings in a patient with ABCA4-related Stargardt's disease shows impaired retinal sensitivity and the location of a preferred retinal locus. Fixation stability of the preferred retinal locus, calculated using the bivariate contour ellipse area analysis, was graded as unstable in this patient.

In a prospective study analyzing light sensitivity of the macula in 326 eyes with *ABCA4* STGD1, mean sensitivity was worse in the inner rings closest to the fovea and best in the outer ring. This trend was reflected by the distribution of deeply scotomatous points, the percentage of which was highest in the fovea and smallest in the outer ring.[40]

When MP was used to examine the visual function of flecked areas, a significant difference in mean retinal sensitivity was found between flecked areas and unflecked areas, with most flecked areas having a decrease in sensitivity.[41] SD-OCT in the flecked areas also revealed hyper-reflective dome-shaped lesions in the RPE, with disruption of the photoreceptor layer.[41]

As a result of macular atrophy, patients with Stargardt's disease develop eccentric and unstable fixation, leading to difficulties reading despite fairly good visual acuity.[42] They also adopt PRLs in a spared area of the retina. MP is a useful tool for identifying these PRLs and examining fixation stability together with other functional measures such as sensitivity (*Figure 4*).

In a multimodal analysis of the PRL in Stargardt's disease, eccentric PRLs located at the edge of central macular atrophy were associated with intact ellipsoid zone (EZ) band, and normal fundus autofluorescence (AF).[43] PRLs located further from the border of macular atrophy had a transition zone, which was associated with decreased sensitivity, absence or disruption of the EZ band, and abnormal FAF patterns.[43]

Thus, the relative position of the PRL to the edge of the macular atrophy in Stargardt's can be a predictor of the structural integrity of the region between the edge of the

macular atrophy and the PRL.

A recent study demonstrated that biofeedback techniques can be inculcated into microperimetric testings for rehabilitation in patients with STGD.[44] The study showed significant improvements in fixation stability, mean BCVA, mean reading speed and contrast sensitivity for subjects with biofeedback training sessions.[44] This demonstrates the potential role of MP for therapeutic training in managing retinal degeneration in Stargardt's disease.

Conclusion

Visual acuity on its own is not a sensitive indicator of visual function in retinal degenerative diseases. Growing evidence supports the use of MP as a clinical and research tool. Its ability to compensate for eye movements, identify preferred retinal loci, and assess fixation stability enhances its utility in diagnosing and monitoring disease progression.

Microperimetric measurements of retinal sensitivity and fixation stability can detect early stages of disease and evaluate clinical outcomes for therapeutic interventions. Hence, MP is well suited for patients with extrafoveal or unstable fixation, and should be considered an important component of functional testing in assessing retinal degenerative conditions. RS

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IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

A New Vision

for your patients with an inherited retinal disease (IRD)

LUXTURNA (voretigene neparvovec-rzyl) is a one-time gene therapy that improves functional vision in individuals with an IRD who have confirmed biallelic *RPE65* gene mutations and viable retinal cells.[1]

With LUXTURNA, patients experienced a clinically meaningful improvement in the ability to navigate at lower light levels.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity
Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the following pages.

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

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P-RPE65-US-360005 April 2018

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Brief Summary of US Full Prescribing Information for LUXTURNA (voretigene neparvovec-rzyl)

1 INDICATIONS AND USAGE
LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis
Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity
Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities
Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. *[See Dosage and Administration (2.3) in full prescribing information]*

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure
Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles
Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract
Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

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

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5×10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety *[see Clinical Studies (14) in full prescribing information]*. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity
At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential
No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 *[see Clinical Studies (14) in full prescribing information]* that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use
The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION
Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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Focus on Imaging

HOW IMAGING IS IMPROVING OUR VIEW OF MMD

Various modalities of optical coherence tomography are revealing findings of myopic macular degeneration we could never see before.

By Chee Wai Wong, MMed (Ophth), FAMS, Gemmy Cheung, PhD, FRCOphth, and Tien Yin Wong, PhD, FRANZCO.

Myopic macular degeneration (MMD) has emerged as one of the leading causes of blindness or low vision in developed nations, particularly in East Asia, where the prevalence of myopia is high.[1,2] It is characterized by choroidal thinning, chorioretinal atrophy and choroidal neovascularization.[3] Because a large proportion of MMD affects young and middle-aged working adults,[4,5] MMD carries a disproportionate socio-economic burden compared to other retinal conditions such as age-related macular degeneration.[6,7,8] Furthermore, many eyes with MMD may develop choroidal neovascular membrane (mCNV), which can also lead to significant visual loss.

Until recently, the burden, definition, clinical features and natural course of this debilitating condition have been poorly understood, but long-term, follow-up clinical studies and advances in ocular imaging have enabled significant progress in our understanding of the disease mechanisms and natural history of MMD. The following imaging modalities have contributed to our knowledge of MMD:

- ***Spectral-domain optical coherence tomography (SD-OCT)*** has enabled the visualization of the retinal pigment epithelium and Bruch's membrane.
- ***Swept-source OCT (SS-OCT)*** has provided greater resolution for the imaging of the deep choroid and sclera in pathologic myopia.[9]
- ***OCT angiography (OCT-A)*** has further allowed for the noninvasive imaging of the retinal and choroidal circulation and has provided new insights into MMD pathogenesis.[10]
- ***Widefield angiography*** has revealed vascular anomalies in the highly myopic eye.
- ***Widefield fluorescein angiography*** has captured areas of nonperfusion in the peripheral retina.
- ***Widefield indocyanine green angiography*** has demonstrated the posterior migration of vortex veins.[11,12]
- ***Widefield fundus photography and widefield OCT*** will likely set future standards for imaging of posterior staphyloma in highly myopic eyes.[13,14]

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Disclosures: Professor Tien Yin Wong is a consultant to and serves on the advisory boards of Allergan, Bayer, Genentech, Novartis and Roche.

Imaging Characteristics of Myopic Macular Degeneration

	Fundus appearance	Fluorescein angiography	Indocyanine green angiography	Optical coherence tomography
Tessellated fundus (Category 1)	Large choroidal vessels visible	Normal	Normal	Thin choroid; Bruch's membrane and retinal pigment epithelium intact
Diffuse atrophy (Category 2)	Ill-defined, yellowish-white appearance	Mild hyperfluorescence from tissue staining	Decrease of choroidal capillary and medium and large choroidal vessels	Thin choroid; Bruch's membrane and RPE intact
Patchy atrophy (Category 3)	Well-demarcated whitish lesion	Hypofluorescence	Hypofluorescence	Absence of RPE-Bruch's membrane-choriocapillaris complex
Macular atrophy (Category 4)	Well demarcated whitish lesion centered on fovea	Hypofluorescence	Hypofluorescence	Absence of RPE-Bruch's membrane-choriocapillaris complex
Plus Signs				
Lacquer crack	Yellowish linear lesions	Linear hyperfluorescence	Linear hypofluorescence	Small gap in Bruch's membrane
Fuchs spot	Grayish-white, sometimes pigmented spot	Early hyperfluorescence decreasing in intensity with time	Hypofluorescence	Subretinal hyper-reflective lesion with well-demarcated margins
Myopic choroidal neovascularization	Small grayish subretinal lesion at or near fovea, with or without hemorrhage	Early hyperfluorescence increasing in size and intensity with time	Late hyperfluorescence	Ill-defined subretinal hyper-reflective lesion with or without subretinal fluid

In this review, we describe the definition, pathogenesis, clinical features and imaging aspects of and potential treatment options for MMD.

Definition and Classification

Earlier studies on the epidemiology of MMD were hampered by a lack of both a consistent definition and a unified classification. Several classifications and definitions existed, but none of them considered the natural history and progression of MMD.[15-17] The lack of a common classification made it difficult to perform direct comparison or pooling of data from different studies to evaluate the prevalence, incidence and risk factors for MMD.

To resolve this issue, the META-analysis for Pathologic Myopia (META-PM) group, proposed a classification system of MMD in five categories (*Table*):

- 0, no myopic retinal lesions;
- 1, tessellated fundus only;
- 2, diffuse chorioretinal atrophy;
- 3, patchy chorioretinal atrophy; and
- 4, macular atrophy.

These categories were defined based on long-term clinical observation that informed on the progression patterns and risk of myopic choroidal neovascularization development for each stage.

Three additional features, observed to occur in any category of MMD, were included as "plus signs:"

- lacquer cracks;
- mCNV; and
- Fuchs spot.

This classification system has been adopted in recent studies and has shown good intra- and inter-grader reliability.[10,18,19]

Take-home Point

Myopic macular degeneration (MMD) is a sight-threatening complication of high myopia. Its rise as a leading global cause of visual loss is of great concern, particularly as the young highly myopic population ages. Our knowledge of this disease has increased over the past decade thanks to long-term clinical trials and advances in ocular imaging, although a lack of effective treatment remains. This article reviews the definition, pathogenesis, clinical features and imaging aspects of MMD as well as potential treatment options.

Rapidly Escalating Incidence

The prevalence of high myopia and related visual impairment is rapidly escalating. A systematic review and meta-analysis of the prevalence of myopia and high myopia found an estimated 163 million people with high myopia (2.7 percent of the

world population) in the year 2000. This number is predicted to grow to 938 million (9.8 percent of the world population) by the year 2050.[2]

Another report estimated that 10 million people suffered from MMD-related visual impairment in 2015 (prevalence 0.13 percent, 95 percent confidence interval [CI] 5.5 to 23.7 million, 0.07 to 0.34 percent), 3.3 million of whom were blind (0.04 percent, 1.8 to 7.8 million, CI 0.03 to 0.10 percent).

By 2050, 55.7 million people will be visually impaired as a result of MMD (0.57 percent, 29 to 119.7 million, 95 percent CI 0.33 to 1.11 percent). Among them, 18.5 million will be blind (0.19 percent, 9.6 to 39.7 million, 95 percent CI 0.11 to 0.37 percent).[20]

Recent population-based studies have used the META-PM classification for myopic maculopathy to analyze the incidence and progression of myopic maculopathy.

In the Handan Eye Study (n=5,394), the five-year incidence of myopic maculopathy was 0.05 percent (95 percent CI 0.02 to 0.10 percent) and progression occurred in 35.3 percent.[21] The Beijing Eye Study (n=4,439) found a similar progression rate of 35.5 percent, but over a longer 10-year period.[22] In the Chinese American Eye Study, the prevalence of any MMD was 32.2 percent, and was higher among older subjects, those with more severe myopia and longer axial length.[23] Data from the IRIS registry and the National Health and Nutrition Examination Survey (NHANES) indicated a diopter-adjusted prevalence of high myopia, progressive high myopia and mCNV of 3.92 percent.[24]

Clinical and Imaging Features

The table describes the imaging features of MMD under the META-PM classification.

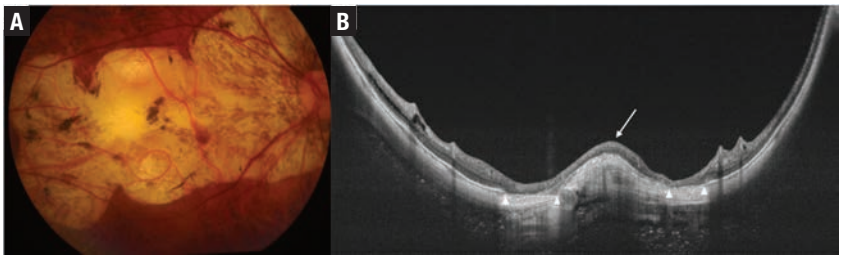

Figure 1. Fundus photograph and swept-source optical coherence tomographic (SS-OCT) scan of the left eye of a patient with Category 4 myopic maculopathy. Fundus photograph (A) shows a large, well-defined yellowish-white lesion involving the fovea and most of the macula, representing confluent areas of patchy chorioretinal atrophy. Choroidal and scleral vessels can be seen coursing through atrophic areas. The SS-OCT scan (B) shows a dome-shaped macula (arrow) with loss of the choroid-Bruch's membrane-retinal pigment epithelium complex on either side of the dome. Increased transmission of light signal (arrow heads) into the sclera and orbital fat can be seen corresponding to areas of complete loss of the retinal pigment epithelium.

• ***Tessellated fundus (Category 1)*** represents the most subtle and earliest clinical features of MMD. In the tessellated fundus, choroidal vessels can be observed clearly around the fovea as well as around the retinal vascular arcade on fundus photography. The choroid appears thin on OCT but the outer retina, RPE and Bruch's membrane are intact.[1]

• ***Diffuse chorioretinal atrophy (Category 2)*** presents as an ill-defined yellowish-white appearance of the posterior pole on fundus photography. The atrophy usually begins in the temporal peripapillary region and increases with age to involve the posterior pole. On fundus fluorescein angiography, mild hyperfluorescence from tissue staining is seen in the late phase. On indocyanine green angiography, a marked decrease of the choroidal capillary and medium and large-sized choroidal vessels has been described within the area of diffuse atrophy.[25] OCT shows marked choroidal thinning, but the outer retinal layers and RPE remain intact.

OCT-A has shown variability in the degree of choriocapillaris flow-signal loss, ranging from no apparent loss to extensive loss with unmasking of underlying large choroidal vessels.[10]

• ***Patchy chorioretinal atrophy (Category 3)*** (*Figure 1*) is characterized by a complete absence of the choriocapillaris, eventually progressing to a loss of the outer retina and retinal pigment epithelium, although the inner retina remains largely intact. Clinically, patchy chorioretinal atrophy appears as clearly demarcated, lobular grayish-white lesions in the macula, representing areas in which the sclera can be seen through the transparent retina. Pigment clumping may be observed within the area of patchy atrophy.

On autofluorescence imaging, these areas show hypoautofluorescence from the loss of RPE. The lesion appears hypofluorescent on FA and ICGA due to choroidal filling defect. Absence of the retinal pigment epithelium can be identified as areas of increased transmission of signal into the underlying sclera on OCT, allowing clear visualization of the scleral contour, episclera and orbital fat. The entire choroid, with the exception of large choroidal ves-

sels, is absent. These areas may be associated with loss of the outer retina with a bridge of inner retina, but in most instances the inner retina can be seen to rest directly on the scleral bed. Occasionally, the inner retina may herniate into the sclera, presumably in areas of scleral ectasia.[25,26]

• ***Macular atrophy (Category 4)*** is a clearly demarcated, grayish-white or whitish, atrophic chorioretinal lesion centered on the fovea. The imaging characteristics are similar to those of patchy chorioretinal atrophy. A well-defined subretinal hyper-reflective lesion representing the fibrotic remains of a regressed CNV may sometimes appear on OCT. The majority of macular atrophy develops from mCNV, with only a small percentage related to expansion of patchy atrophy.[26,27]

Progression of MMD

The longest follow-up study to date found a progression rate of 47:1,000 eye-years among 810 eyes of 432 patients in a hospital-based population.[27] The progression rate was highest in eyes with macular atrophy at baseline, followed by patchy atrophy, diffuse atrophy and myopic eyes without MMD.

Risk factors for progression were: female gender; longer axial length; greater axial elongation; and development of parapapillary atrophy.

In the earlier stages of MMD, the predominant process is progressive choroidal thinning (*Figure* 2) from tessellated fundus (Category 1) to diffuse atrophy (Category 2). Diffuse atrophy tends to start in the parapapillary region and expands to involve the macula.

Breaks in Bruch's membrane are the main drivers for progression to the more severe grades of MMD. These breaks can arise from lacquer cracks or myopic CNV. Patchy atrophy (Category 3) develops around lacquer cracks and may expand to involve the fovea (patchy related macular atrophy, Category 4). Atrophy developing around the site of a regressed myopic CNV is thought to be due to rupture of Bruch's membrane, and is the main cause of macular atrophy (Category 4).

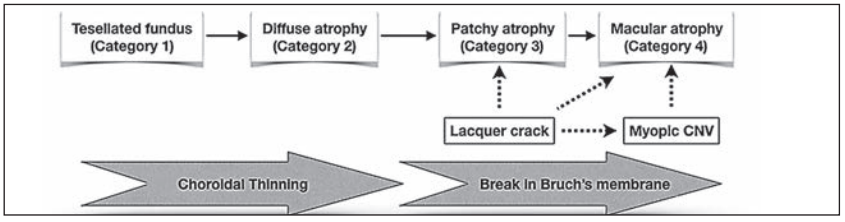

Figure 2. Progression of myopic macular degeneration (MMD) reveals increasing thinning of the choroid from tessellated fundus (Category 1) to diffuse chorioretinal atrophy (Category 2). Bruch's membrane breaks trigger progression to the late stages of myopic macular degeneration. Patchy chorioretinal atrophy (Category 3) develops around lacquer cracks and may progress to patchy related macular atrophy (Category 4), although in most cases, myopic CNV-related macular atrophy is the cause of Category 4 MMD.

Plus Signs of MMD

• ***Lacquer cracks*** are thought to be mechanical breaks of the Bruch's membrane. Clinically they appear as yellowish linear lesions, sometimes in a stellate pattern, in the macula. Lacquer cracks are difficult to discern on clinical examination or fundus photography alone. ICGA is widely accepted as the best method for detecting lacquer cracks, which typically appear as linear hypofluorescence in the late phase of ICGA.[25] Subretinal bleeding is often observed at the onset of lacquer cracks, but is usually absorbed spontaneously with good visual recovery.

It is worth noting that myopic CNV may develop at sites of lacquer cracks as well; thus, FFA and OCT should be performed in cases of subretinal bleeding when clinical suspicion merits it.[25]

• ***mCNV*** (*Figure* 3) appears on clinical examination as a small grayish subretinal lesion at or near the fovea, with or without hemorrhage. mCNV evolves from the active stage to scarred stage (Fuchs spot) and, finally, atrophic stage.[28] The diagnosis is confirmed on fundus fluorescein angiogram where the lesion demonstrates hyperfluorescence that increases in size and intensity with time, indicating leakage.[29]

On OCT, mCNV appears as a subretinal hyper-reflective lesion, with or without subretinal fluid. OCT appearance is helpful to determine the stage of mCNV. Signs of activity include ill-defined margins[25] and disruption of the external limiting membrane,[30] with a variable amount of intraretinal or subretinal fluid.

With treatment, the hyper-reflective lesion consolidates and acquires a distinct border. OCT-A is useful for identifying the choroidal neovascular membrane noninvasively.[31,32] However, OCT-A has lower sensitivity compared to FFA, and cannot replace the latter as the diagnostic gold standard.[33]

Another limitation of OCT-A is the lack of information on disease activity. Flow-signal may persist in an inactive mCNV; therefore OCT and FFA are still required to monitor the level of activity.[32-34] mCNV responds remarkably well to treatment with intravitreal anti-VEGF agents, often

requiring only a few injections for disease control.[35] Chorioretinal atrophy may develop around the CNV lesion, particularly if left untreated, leading to macular atrophy and eventual visual loss.[36,37] Studies have revealed that macular atrophy developing after mCNV may be the result of a Bruch's membrane rupture.[36]

• ***Fuchs spot*** is a grayish-white, sometimes pigmented lesion representing the scar phase of myopic CNV.[3] Accordingly, the lesion stains but does not leak on FFA. On OCT, Fuchs spot appears as a subretinal hyper-reflective lesion with sharply delineated borders not associated with exudation.

• ***Posterior staphyloma*** (*Figure 4, page 36*) is a key lesion of pathologic myopia. With the advent of SD-OCT, Richard Spaide, MD, defined staphyloma as an outpouching of the wall of the eye that has a radius of curvature less than the surrounding curvature of the eye wall itself.[38] Clinically, posterior staphyloma can be identified on binocular indirect ophthalmoscopy by an abrupt change in the retinal surface contour posteriorly.

Fundus photographs are not ideal for the assessment of posterior staphyloma because they lack depth perception and often do not encompass the full width of the staphyloma. Widefield fundus imaging, which can image up to 200 degrees of the retina, can partly address this limitation. Three-dimensional MRI is an effective method of visualizing the posterior staphyloma, but is cumbersome and expensive to perform.

Kyoko Ohno Matsui, MD, employed a combination 3D-MRI and widefield fundus images to characterize the different types of posterior staphyloma, and found that wide macular staphyloma was the most common, followed by narrow macular staphyloma.[39] SS-OCT volume scans with a maximum scan width of 12 mm through the macula and optic disc can be reconstructed three-dimensionally and allow some appreciation of the posterior globe contour, although this method is still limited by its scan width. Anthony Kuo, MD, and colleagues, including members of our group, reported that distortion-corrected OCT measurements of the posterior eye radius of curvature and asphericity were comparable to values obtained from 3D-MRI and could potentially be used to study posterior eye shape.[40]

Widefield OCT may offer an easier way to characterize posterior staphyloma. A multinational study led by Kosei Shinohara, MD, showed that WF-OCT was equivalent to 3D-MRI in detecting posterior staphyloma, and additionally allowed the study of spatial relationships between the staphyloma, the optic nerve and the retinal structures.[13]

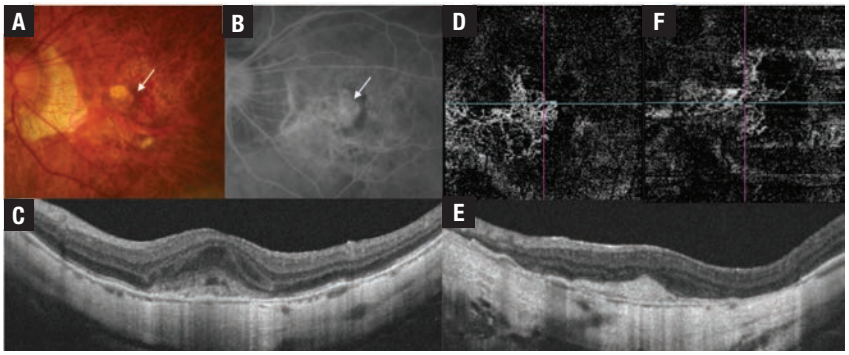

Figure 3. Multimodal imaging of myopic choroidal neovascularization (mCNV) before and after treatment with intravitreal anti-VEGF injections. Fundus photograph (A) shows a dark red patch of subretinal hemorrhage (arrow). Corresponding fundus fluorescein angiogram (B) shows early hyperfluorescence in a lacy pattern in the subfoveal location (arrow). Swept-source optical coherence tomography (C) shows a subretinal hyper-reflective lesion with indistinct margins. A 3-by-3-mm OCT angiography scan (D) through the outer retina segment shows a network of vessels representing the mCNV lesion. After treatment with four anti-VEGF injections, the mCNV lesion (E) has acquired a distinct border and subretinal fluid is absent. Flow signals persist in the inactive mCNV lesion (F), but the vessel network appears to be less dense compared with the pre-treatment OCT-A.

Pathogenesis of MMD

The mechanisms that lead to the development of the macular and retinal changes in MMD remain hypothetical.[25] A widely accepted view is the "mechanical" theory of MMD in which axial elongation of the globe from scleral remodeling results in the mechanical stretching of the retina, leading to decreased photoreceptor density and pathologic features such as lacquer cracks and chorioretinal atrophy.[41]

In addition to the "mechanical" theory, some authors have suggested that choroidal thinning, leading to decreased choroidal perfusion and ischemia and subsequent upregulation of angiogenic factors in some eyes, may also be a mechanism for the development of myopic choroidal neovascularization and atrophy of the outer retinal layers as seen in MMD.[42] Authors have observed histological evidence of choroidal vessel narrowing and loss in highly myopic eyes.[43] Parapapillary diffuse choroidal atrophy in children, a risk factor

for future development of MMD, is associated with extreme thinning of the parapapillary choroid.[44] Our previous studies in choroidal imaging have demonstrated:

- a stronger association of choroidal thickness with MMD compared to scleral thickness (a proxy for mechanical stretching); and
- altered choriocapillaris flow in eyes with MMD, lending further credence to this theory.[10,19]

Another theory holds that Bruch's membrane production at the retro-equatorial region results in axial elongation.[45] The expanding Bruch's membrane actively compresses the choroid against the sclera which stretches passively to a certain degree.

In this manner, the Bruch's membrane drives both the mechanical stretching and attenuation of the vascular supply to the outer retinal layers. Areas of patchy atrophy have been observed to be devoid of Bruch's membrane, suggesting that patchy atrophy may represent expansions of Bruch's membrane defects as the globe continues to elongate axially.

Role of Anti-VEGF

While significant progress has been made in understanding the clinical features of MMD, unfortunately, no effective therapies to prevent or treat the many stages of established MMD exist.

The major exception is mCNV. The RADIANCE trial compared two different dosing regimens of ranibizumab (Lucentis, Roche/Genentech)—at day one, month one and PRN; and day one and then PRN—vs. verteporfin photodynamic therapy (Visudyne, Bausch + Lomb). Visual acuity outcomes were significantly better in both dosing regimens of ranibizumab: mean visual-acuity gain of 13.8 and 14.4 letters from baseline in the respective ranibizumab treatment groups vs. gains of 9.3 letters in the PDT group at 12 months.[46]

In the MYRROR study, intravitreal aflibercept (Eylea, Regeneron) was found to be effective for the treatment of mCNV, achieving an average of 13.5 letters gained at 48 weeks compared to 3.5 letters in the group that received sham injections through week 20 and then aflibercept.[47] These two major trials have established intravitreal anti-VEGF injections as the first-line treatment for mCNV.[48,49]

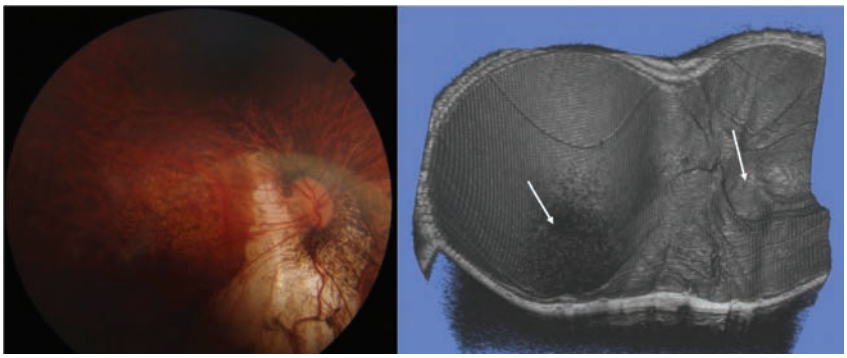

Figure 4. Fundus photograph and swept-source optical coherence tomographic scan of a patient with compound posterior staphyloma. Reconstruction of the 12-by-9-mm scans into a three-dimensional image (right) clearly shows a compound posterior staphyloma with two apices, one at the optic nerve head and another centered on the fovea (arrows).

What Hinders New Treatments

Several challenges hinder the development of therapies for MMD. First, the etiology of MMD is still not well understood. In particular, it is unclear whether childhood myopia will eventually develop into pathologic myopia in adulthood. Some evidence indicates that parapapillary diffuse chorioretinal atrophy in highly myopic children can be a potential biomarker for the eventual development of MMD in adulthood.[50] This suggests that eyes at high risk of MMD may be fundamentally different from eyes with simple myopia. This leads to the question of whether controlling myopia progression alone is sufficient to prevent MMD in these eyes.

Second, uncertainty surrounds the optimal time for treatment, although clinicians agree that treatment should be initiated before clinically apparent and irreversible atrophy occurs. We have previously demonstrated that OCT-A may be a useful tool to identify choriocapillaris changes in eyes with no or early MMD.[50] However, these findings will need to be validated in prospective studies.

That brings us to the next problem: MMD progression occurs over a prolonged period of time, thus complicating the assessment of treatment effects. Large cohorts will have to be monitored for many years, and this can only be achieved by the combined efforts of an international research consortium.

Further research will have to be undertaken to overcome these challenges but, in the meantime, efforts to reduce the overall disease burden should continue. Further advance-

ments in imaging technology and treatment will accelerate the search for an effective MMD treatment.

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Management of MMD In Children and Adults

Until further research leads to improved treatments for myopic macular degeneration, clinicians can help to reduce disease burden.

In children, myopia control is obviously of utmost importance. The public should be educated on the various complications of high myopia and the need to seek eye care early if a child's vision deteriorates.

In adults, choroidal neovascular membrane should be treated urgently until the disease activity resolves completely to reduce the risk of chorioretinal atrophy developing around the CNV lesion.[35]

Research in recent years has shifted from purely focusing on simple childhood myopia to adult pathologic myopia and MMD, but clearly, more needs to be done to address the future public-health threat of MMD.

HOW TECHNOLOGY HAS HUMANIZED LOW-VISION AIDS

The days of bulky overhead readers and magnifiers are over, thanks to smartphone, tablet, laptop and desktop technology.

By Dorrie Rush

Imagine what it is like to be shut out of a major event, then suddenly the doors open. The opportunity to be like everyone else, in this respect, is life changing. For people with vision loss, the ability to perform daily functions had been limited by their access to bulky overhead readers and thick magnifiers, but those days are over. Thanks to the evolution of technology, the doors are opening for these individuals. They can now perform visual tasks inconspicuously.

This technology evolution has been happening for more than a decade, driven by inclusive design, universal access and the needs of an aging demographic. So now that the technology is universal, the awareness should be as well. Here is a brief overview to bring the retina specialist up to speed on where we are and how we got here.

Apple Accessibility

In 2008, the fully accessible iPhone 3s came to market. This was the first smartphone designed to accommodate the entire spectrum of vision loss. The accessibility settings on the iPhone included large text, zoom, invert colors and VoiceOver, a full-function screen reader (*Figure 1*). It was a pivotal moment: a popular consumer product, with built-in accessibility ready to go right out of the box at no extra cost.

As the mobile operating system developed, the visual accessibility tools developed with it. In many ways the regular features that evolved in the iPhone were a boon to people who are visually impaired. Dictation allows everyone to avoid typing on the keyboard by turning speech to text. Siri was our first experience with a digital assistant driven by artificial intelligence, which initiated an era unto itself.

In 2018, the iPhone is the most common denominator among people with vision loss. Although all smartphones now come off the shelf with accessibility requirements, Apple's attention to inclusive design, technical and customer support is unparalleled.

Extra apps can add even more function. Convert the camera to a high-definition magnifier (*Figure 2, page 40*), document scanner, product identifier or sign reader. Get walking directions from the digital assistant using Maps, find the right way with Compass, have the newspaper read aloud or dictate a shopping list into reminders. There is a flashlight always on hand, a book reader, transit tracker, banking, contacts and much more. Think of it as

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100 low-vision devices in one.The iPad, iPod Touch, Apple Watch, Apple TV and the Mac also come with the same standard functions for visual and non-visual access.

Microsoft

Microsoft is also committed to accessibility more than ever. The Windows operating system has vastly improved its built-in accessibility options for people with visual impairments. The adjustments users need to make in terms of magnification, contrast and speech can be accomplished with a little help from their IT department. For low-vision users, this largely eliminates what once was an inevitably awkward conversation with an employer requesting complicated, expensive and often unsupported assistive software. Requiring some adjustments at work to personalize visual settings is not at all unusual today.

Recently, Microsoft made another move to progress mobile accessibility, but not for its own product. The company built two groundbreaking apps for the iPhone and put them on the Apple App Store for free. They are:

- ***Seeing AI***, accessed more than 1 million times in its first six months, offers multiple channels that identify short text, documents, people, products, handwriting and more. Some of the features are in development and keep improving. For low-vision users, the short text feature is a dream come true; just point the phone at text and it instantly starts reading.
- ***Soundscape*** is billed as a "map with 3D sound." This technology incorporates GPS to give visually impaired and blind users enhanced information about their surroundings. It's a bit like strolling along with a friend who is telling you about your environment and calling out streets and intersections on your rout.

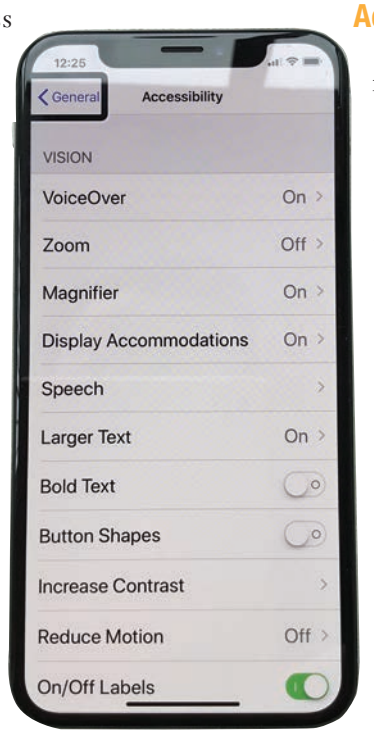

Figure 1. Accessibility settings on the iPhone include multiple selections to improve function for people with visual impairment.

Accessibility Support

Apple continued to remove barriers by implementing a phone support line dedicated to accessibility, further empowering customers with visual, hearing, motor and learning impairments. It soon went from a limited number of hours each day to 24/7.

In relatively short order, Microsoft launched the Disability Answer Desk. Verizon Wireless and Comcast opened their own accessibility support centers. Amazon's technical support specialists are well versed in accessibility.

Quotable

The 21st Century Communications and Video Accessibility Act, signed in 2010, requires digital, broadband and mobile technologies be accessible to people with disabilities.

Google is reportedly preparing to roll out its own accessibility support phone service soon.

CVAA Pushes the Envelope

It would only be fair to call out the influence of the 21st Century Communications and Video Accessibility Act, signed in 2010 to update federal laws to require advanced communications products and services, including digital, broadband and mobile technologies, be accessible to people with disabilities. The requirements, which were phased in over a period of years, address the accessibility of mobile browsers, descriptive video, on-screen menus and TV program guides.

Although the rules of the CVAA were neither strict nor specific, the

Take-home Point

Smartphones, tablets, laptops and desktops now include built-in accessibility options that help people who are visually impaired function inconspicuously, a far cry from the bulky, obtrusive low-vision aids. This article reviews the advances in technologies and apps, including smart speakers, smart television and even descriptive audio, along with support services that are making life easier for people with low vision.

Figure 2. The inconspicuous smartphone magnifier.

technology makers of note seem to have stepped up and continue to deliver.

Amazon

Not always the bastion of accessibility, Amazon is undeniably the most improved in this category. All Kindle e-readers and Fire tablets offer an array of options to adjust text and display settings, or to use VoiceView, the screen reader for non-visual access. Magnification is available in the tablets, as is Alexa, the digital assistant.

Smart Speakers and Digital Assistants

The advent of artificial intelligence is driving interactivity into an entirely new realm. No reading or typing required, just talking. Digital assistants in smartphones have quickly gained traction, particularly for people living with vision loss. Just ask for the news, weather, audiobooks, podcasts, time and timers. Or you can play games, order an Uber, calculate math or ask an endless number of interesting questions.

Perhaps Amazon's greatest contribution to accessibility is the Echo speaker with Alexa. Smart speakers are already being adopted at a rate faster than smartphones, and they are accessible to everyone who has a voice. For the moment the smart speaker business is dominated by Amazon, with Google Home and Apple's Home Pod and others vying for a bigger piece of the action. Amazon, Google and Apple all have phone support available to help in the setup and use of their smart speakers.

Android

Phones and tablets with Android operating systems can be counted on for advanced visual accessibility, although not universally as well supported or user friendly as Apple's offerings.

Recently Google announced an accessibility app in development for Android called Lookout. It's designed to provide auditory cues about your surroundings and to read text. It will be available by year's end on Google Play.

Accessible TV and Movies

The CVAA now requires cable television providers to supply voice-enabled on-screen menus and television guides to visually impaired customers. This accommodation can be achieved in a number of ways, including the use of apps and smart speakers.

Comcast offers the most comprehensive services. They include talking menus, voice search and a dedicated accessibility support center. Descriptive audio is also now available for moviegoers who are unable to clearly see the big picture. An embedded track is woven into the quiet spaces, describing the visual details of the film that might otherwise be missed. Theaters are now required to have listening devices available upon request. Descriptive audio can also be accessed on mobile devices and smart TVs with a selection in settings.

While technology to aid the visually impaired has come far in the past few years, this is just the beginning. There is much more to come. Stay tuned and be aware. RS

RETINA STANDOUTS FROM ASRS 2018

WHAT'S NEW IN GA MANAGEMENT AND MORE

Plus early results of flanged IOLs, PRP vs. IVT for patients lost to follow-up and LADDER Trial results of port delivery.

By Ashkan M. Abbey, MD

The annual meeting of the American Society of Retina Specialists in Vancouver provided a wide variety of innovations in diagnostics, treatment and management strategies for retinal disease. With so many impressive presentations and posters this year, the task of choosing five of the more intriguing abstracts to highlight is extremely challenging, while also inspiring great confidence in the future of our field.

Here, we summarize five of the most interesting presentations. They include a new medication for the slowing of geographic atrophy, the subretinal injection of a bioengineered retinal pigment epithelium monolayer for advanced GA, the utility and safety of flanged haptics in sutureless scleral fixation of intraocular lenses, the outcomes of patients with proliferative diabetic retinopathy after being lost to follow-up, and the use of a port delivery system (PDS) for neovascular age-related macular degeneration.

Complement C3 Inhibitor for GA

The treatment of GA in AMD has perplexed retina specialists for decades. Fortunately, there appears to be significant promise with APL-2 (Apellis Pharmaceuticals), a complement C3 inhibitor, in slowing the growth of GA. APL-2, or pegcetacoplan 15 mg, is a synthetic cyclic peptide conjugated to a polyethylene glycol polymer that binds specifically to C3 in the complement pathway. C3 resides far "upstream" in the complement pathway; thus, its inhibition by APL-2 impedes all three pathways of complement activation—classical, lectin and alternative.

In this prospective, randomized, sham-controlled, single-masked Phase II trial,[1] patients with GA area measuring 2.5 to 17.5 mm^2 and best-corrected visual acuity of $\geq$24 letters (20/320 Snellen equivalent) were randomized to four arms: APL-2 monthly (n=86); APL-2 every other month (EOM; n=79); sham monthly (n=41); and sham EOM (n=40). The patients were treated for 12 months, followed by six months of

Take-home Point

Five presentations from the American Society of Retina Specialists 2018 meeting caught our contributing editor's attention: Phase II trial results of a complement C3 inhibitor to treat geographic atrophy (GA); interim results of a bioengineered retinal pigment epithelium monolayer for advanced GA; a retrospective case review of sutureless intrascleral fixation using an intraocular lens with flanged haptics; a retrospective study comparing intravitreal anti-VEGF therapy with panretinal photocoagulation diabetic retinopathy patients lost to follow-up; and results of the Port Delivery System for neovascular AMD.

ABOUT THE AUTHOR

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DISCLOSURE: Dr. Abbey is a consultant for Allergan and Genentech.

observation. The primary outcome was the difference in mean change from baseline in square-root GA area based on fundus autofluorescence at 12 months.

At 12 months, monthly APL-2 slowed GA growth by 29 percent (p=0.008), and EOM APL-2 slowed GA growth by 20 percent (p=0.067) vs. sham. In the final six months of treatment, the results were even more impressive. Monthly APL-2 slowed GA growth by 47 percent (p<0.001) and EOM APL-2 slowed GA growth by 33 percent (p=0.01) vs. sham. When treatment was stopped after 12 months, rates of GA progression were similar among the treatment and sham groups.

A potentially concerning finding was a higher rate of conversion to neovascular AMD in the treatment groups: 20.9 percent in the APL-2 monthly group; 8.9 percent in the APL-2 EOM group; and 1.2 percent in the sham pooled group.

Previous attempts at targeting the complement pathway to slow the progression of GA in AMD have failed. However, this Phase II trial of APL-2 has shown impressive results, and the retina community hopes it becomes the first Food and Drug Administration-approved treatment for GA. The higher rates of conversion to nAMD in the treatment groups are concerning, but larger trials are needed to understand the possible association with choroidal neovascularization. Phase III clinical trials will begin this year.

Stem Cell RPE Monolayer

APL-2 may help to slow growth of GA, but it doesn't result in any improvement to the area where the RPE has already been lost. Amir Kashani, MD, and colleagues aimed potentially to improve vision in patients with GA by implanting a monolayer of RPE under the retina.[2]

They created a clinical-grade retinal implant consisting of a polarized monolayer of human embryonic stem cell-derived RPE grown on a synthetic substrate that was designed to mimic Bruch's membrane. They are currently engaged in a Phase I/IIa study to assess the safety and efficacy of a composite subretinal implant in patients with advanced GA.

The interim results analyzed four subjects that successfully received the implant in a surgical procedure. It appeared to be safe and well tolerated. In all four subjects, optical coherence tomography demonstrated integration of the RPE implant with host photoreceptors. None of the eyes demonstrated worsening of vision. Astonishingly, one subject's vision in the implanted eye improved by 17 letters. Two eyes were reported to have improved fixation.

This implant has the potential to be the first treatment for dry AMD that may result in improved vision, a groundbreaking step for a disease that remains without a viable treatment. Additional studies with larger populations are needed to better evaluate its safety and efficacy, but the preliminary results are very encouraging.

27-G Sutureless IOL Fixation

Sutureless intrascleral (SIS) fixation of intraocular lenses has become an increasingly popular surgical technique in eyes with inadequate capsular support. In this study, the authors demonstrated that the additional step of "haptic flanging" helps to minimize postoperative IOL dislocation in these cases. Haptic flanging involves using low-temperature cautery to melt the distal tips of both haptics of the three-piece IOL used for sutureless scleral fixation.

The authors initially performed 27-gauge SIS fixation of a three-piece IOL on five cadaveric human eyes. They compared the force required to dislocate a flanged and unflanged haptic. In these five eyes, flanged haptics required significantly more force to dislocate the IOL than unflanged haptics (14 ±4 vs. 3 ±1 g, p=0.03).

A retrospective review of 52 SIS cases with haptic flanging reported a mean visual acuity gain from 20/140 to 20/50 one month postoperatively (p<0.001). The most common postoperative complication was intraocular pressure rise (n=12, 23 percent).

The additional step of haptic flanging during SIS surgery creates a more stable scleral-fixated IOL compared with the traditional unflanged technique based on the cadaveric human eye study. This study provides valuable data to support haptic flanging to reduce the rate of IOL dislocation.

PRP vs. Anti-VEGF for LTFU

Most retina specialists are well versed in the results of the Diabetic Retinopathy Clinical Research Network Protocol S study, which found that the treatment of proliferative diabetic retinopathy with intravitreal ranibizumab (Lucentis, Roche/Genentech) was non-inferior to panretinal photocoagulation with respect to visual outcomes at two years. In this study, the authors examined a "real-world" scenario that is difficult to evaluate in a prospective clinical trial: loss to follow-up (LTFU) after treatment for PDR.[4]

This retrospective study included 76 eyes of 59 patients who were LTFU for more than six months after initial treatment of either IVT anti-VEGF (30 total eyes) or PRP (46 eyes) for PDR. Between the two treatment groups, the study gathered and compared visual-acuity and

anatomic outcomes at the visit before LTFU, return visit, six- and 12-month visits after return, and the final visit.

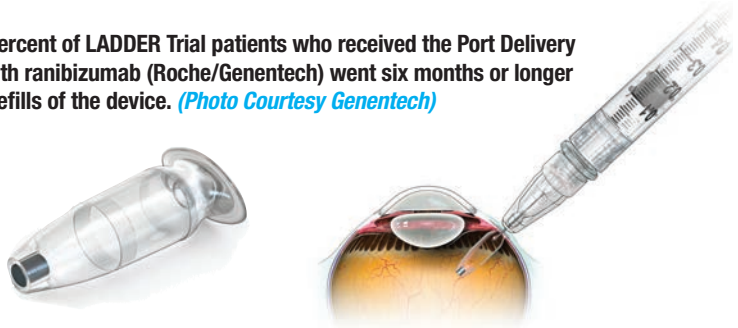
In both the IVT and PRP eyes, mean logMAR VA significantly worsened when comparing the visit before LTFU to the return visit. When comparing VA at the final visit to the visit before LTFU, IVT eyes demonstrated significantly worse VA (0.92 [±0.94], 20/166, p=0.01), while PRP eyes showed no significant difference in VA (0.46 [±0.47] 20/58, p=0.38).

Furthermore, the incidence of tractional retinal detachments was significantly higher in the IVT group at the return visit (five vs. none, p=0.008) and the final visit (10 vs. one, p=0.005). The IVT group also had significantly greater incidence of iris neovascularization at the final visit (four vs. none, p=0.02). Eyes with PDR that received only IVT and were subsequently LTFU demonstrated worse visual and anatomical outcomes than those that received PRP.

These very intriguing findings encourage us not to take the outcomes of a clinical trial such as Protocol S completely at face value. Despite the advantages of IVT compared to PRP for PDR that Protocol S demonstrated (superior improvement in VA in eyes with concurrent diabetic macular edema, less visual field loss and lower rates of vitrectomy), we must note that these outcomes occurred only with regular follow-up and treatment in the context of a well-organized clinical trial.

Unfortunately, the compliance of diabetic patients in our clinics can be far from predictable, as many of them attempt to balance occupational and family obligations with the burden of numerous doctor visits. This study highlights that we must consider the possibility of LTFU when determining treatment—and that we should still consider PRP as a viable treatment option, particularly in patients who are unable to consistently return for appropriate follow-up.

Up to 80 percent of LADDER Trial patients who received the Port Delivery System with ranibizumab (Roche/Genentech) went six months or longer between refills of the device. ***(Photo Courtesy Genentech)***



Ranibizumab PDS

The treatment burden associated with appropriate care of nAMD is a problem that must be addressed in the coming years, particularly with the rapid growth of the aging population in the United States. The Port Delivery System (PDS) with ranibizumab (Roche/Genentech) aims to address this challenge.

The small, refillable PDS implant is inserted at the pars plana in an outpatient procedure and is filled with a concentrated formulation of ranibizumab at the time of surgery. It can subsequently be refilled during a minor office procedure similar to a standard intravitreal injection. Phase II trial results for the PDS show great promise in significantly reducing treatment burden while also maintaining excellent outcomes.

In this prospective, multicenter, randomized, interventional, active treatment-controlled trial,[5] 179 patients were randomized to receive the PDS implant with a dose of either 10 mg/mL (n=58), 40 mg/mL (n=62), or 100 mg/mL (n=59) of ranibizumab. In the 100-mg/mL group, approximately 80 percent went six months or more without needing a refill of medication. In the 10-mg/mL and 40-mg/mL groups, 63.5 percent and 71.3 percent, respectively, went six months or more. When compared to a control group of patients receiving the standard monthly injections of ranibizumab, the 100-mg/mL dose group demonstrated similar improvements in BCVA and reductions in measurements of central retina thickness on OCT. The median time to requiring a refill for the 100 mg/mL group was 15 months.

Both patients and physicians would welcome reducing the need for monthly injections for nAMD. This trial demonstrates that the patients treated with the PDS can achieve visual and anatomic outcomes similar to our current gold-standard treatment of monthly injections. The retina community will be looking forward to the outcomes of the upcoming Phase III trial of this device.

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By Efrem D. Mandelcorn, MD, FRCSC »

Pachychoroid Spectrum: A Closer Look

First described only five years ago, enhanced imaging technology has made it easier to identify and diagnose. ***By Joel Yap, MD, and Efrem D. Mandelcorn, MD, FRCSC***

The pachychoroid spectrum of diseases was first described by David Warrow, MD, and colleagues in 2013, who specified a group of conditions characterized by choroidal thickening and retinal pigment epithelial changes, with or without corresponding retinal abnormalities.[1,2] In increasing visual significance and severity, the four disease groups in the pachychoroid disease spectrum are:

- pachychoroid pigment epitheliopathy (PPE);
- central serous chorioretinopathy (CSCR);
- pachychoroid neovasculopathy (PNV); and
- polypoidal choroidal vasculopathy (PCV).

Here, we review the four groups of the pachychoroid spectrum.

Anatomy of Choroid

Before we discuss each group, it is important to understand the anatomical features of the normal choroid and how the pachychoroid disease spectrum alters them. The choroid is a vascularized and pigmented tissue, which is in continuation with the ciliary body and iris. It surrounds the optic nerve head posteriorly and extends anteriorly to the ora serrata. The choroid has a mean thickness of 0.15 mm anteriorly and 0.22 mm posteriorly.[3] From the outside to inside, the choroid consists of five layers:

- suprachoroid lamina;
- Haller's layer (large choroidal veins);
- Sattler's layer (medium-sized choroidal veins);
- choriocapillaris (fenestrated vessels that supply the outer retina); and
- Bruch's membrane (a thin membrane adjacent to the retinal pigment epithelium).

A structurally and functionally intact choroid is important for normal retinal function, as the choroidal blood supply nourishes the external third of the retina.

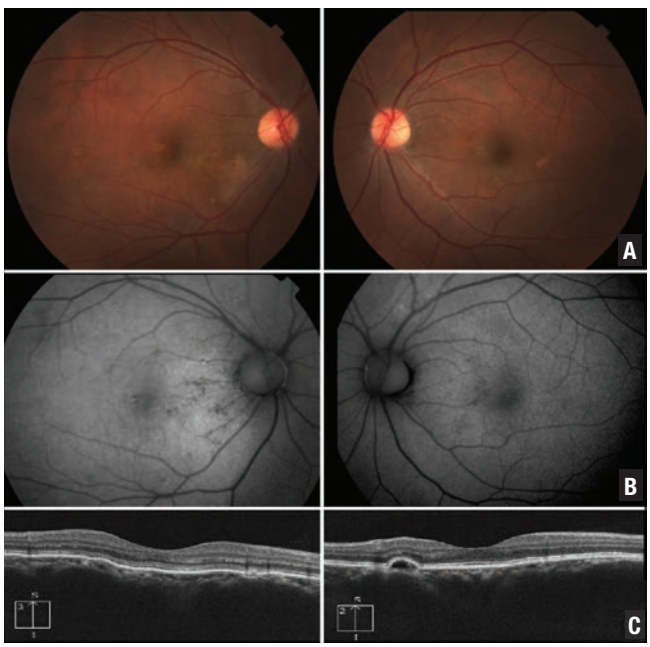

Figure 1. Multimodal imaging of an asymptomatic 44-year-old female patient with pachychoroid pigment epitheliopathy. Fundus photographs (A) of both eyes show bilateral retinal pigment epithelial and pigmentary changes. Fundus autofluorescence (B) demonstrates patches of hyperautofluorescence and hypoautofluorescence at both macular regions. Optical coherence tomography (C) of both eyes reveals a thick choroid bilaterally and a small left parafoveal serous pigment epithelial detachment.

Disease Characteristics

Choroidal thickness varies with age, ethnicity and axial length, and normal mean subfoveal choroidal thickness varies between 191 and 354 µm. A thick choroid, the basis of the "pachychoroid" term, can be defined as a choroidal thickness of >390 µm.[4] Although clinical manifestations of pachychoroid spectrum disorders vary considerably, swept-source optical coherence tomography has shown that they share similar morphological findings in the choroid, namely increased thickness and dilated outer choroidal vessels.[5] With disease chronicity, focal choriocapillaris atrophy with inward displacement of deep choroidal vessels ensues.

The advent of enhanced depth imaging (EDI) OCT, swept-source OCT and fundus autofluorescence has led to greater precision in the diagnosis of pachychoroid-driven diseases, which previously were easy to misdiagnose or overlook.

Pachychoroid Pigment Epitheliopathy

PPE is thought to represent a form fruste or precursor of CSCR, as it has features of retinal pigment epithelium disturbances similar to CSCR but with-

out clinical or imaging evidence of acute or chronic subretinal fluid.[1] It is typically a "silent" disease because patients are frequently asymptomatic. Patients with PPE possess a thickened choroid, appearing clinically as a reddish-orange fundus, with reduced fundus tessellation and a variety of overlying RPE abnormalities including small pigment epithelial detachments.

In the setting of unilateral CSCR, reports have documented PPE findings such as pigmentary changes, asymptomatic PEDs, choroidal hyperpermeability and increased choroidal thickness in the fellow eye, even without serous neurosensory detachment.[6]

Idiopathic serous PEDs have also been implicated as a subtle variant of CSCR.[7] Alphonso Giovannini, MD, and colleagues analyzed indocyanine green angiography videos of 25 patients with idiopathic serous PEDs and found that 83 percent of eyes had evidence of choroidal hyperpermeability.[8] Furthermore, 33 percent of eyes had an irregularly dilated choroidal vein within 1 disc diameter of the PEDs. This finding suggests that a thickened choroid drives the RPE changes seen in PPE.

In the clinical setting, PPE can be identified based on clinical findings and noninvasive tests such as OCT and FAF, as demonstrated by our index case (*Figure 1*). This case involves an asymptomatic 44-year-old woman, who was referred with pigmentary changes in both macular regions. Her investigative findings were consistent with PPE.

A greater awareness of this entity may encourage clinicians to perform these investigations and make the diagnosis earlier, which may ultimately prevent unnecessary diagnostic tests and interventions. Patients with PPE are frequently misdiagnosed as having inactive CSCR, early age-related macular degeneration, macular dystrophies or inflammatory chorioretinopathies such as punctate inner choroidopathy.

The Pachychoroid Disease Spectrum

- Pachychoroid pigment epitheliopathy (PPE)
- Pachychoroid neovasculopathy (PNV)
- Central serous retinopathy (CSR)
- Polypoidal choroidal vasculopathy (PCV)

Central Serous Chorioretinopathy

CSCR is a retinal disorder that occurs in otherwise healthy young or middle-aged patients. The disease is characterized by serous detachment of the neurosensory retina, which is often associated with one or more serous PEDs. In keeping with its inclusion in the pachychoroid disease spectrum, patients with CSCR have a thick choroid, increased choroidal vascular area and increased choroidal vascular permeability.[9,10]

Pigment epithelial detachments may occur in areas of choroidal hyperpermeability, increasing the risk of local RPE disruption, eventually resulting in leakage of serous fluid into the subretinal space. It is not surprising that CSCR risk factors, such as type A personality traits, corticosteroid exposure and pregnancy, are also risk factors for PPE development.[1]

Pachychoroid Neovasculopathy

The PPE and CSCR spectrum of pachychoroid diseases may progress to PNV, a form of Type 1 (sub-RPE) neovascularization occurring over areas of increased choroidal thickness and dilated choroidal vessels. Although the exact mechanism has not been elucidated, authors have theorized it is similar to the process in AMD, in which a break in Bruch's membrane, due to chronic RPE changes and longstanding PEDs, allows the ingrowth of abnormal blood vessels.

Claudine Pang, MD, and colleagues reported a case series of three patients with PNV.[2] Because these patients don't have typical AMD or degenerative changes, they are often diagnosed with choroidal neovascularization from an unknown etiology. In this series, OCT imaging revealed not only choroidal thickening, but also choroidal vascular dilation directly below the neovascular tissue and obliteration of the choriocapillaris and Sattler's layers. Of note, all three patients were younger than the typical age of presentation for AMD-related CNV.

Kunal Dansingani, MD, and colleagues in another study used OCT-A and dye angiography to examine 22 eyes with pachychoroid features and shallow irregular PEDs.[11] They identified PCV in four eyes with dye angiography, and only 29 percent of the remaining eyes demonstrated specific features of neovascularization. In contrast, they also found Type 1 neovascularization on OCT-A in 21 of the 22 study eyes.

Hence, the finding of irregular, shallow PEDs and a thick choroid on OCT has greater diagnostic value for Type 1 neovascularization than previously thought. More importantly, dye angiography may underestimate the presence of neovascularization compared to OCT-A in this disease. Figure 2 (*page 46*) demonstrates the multimodal imaging results of one of the patients Dr. Dansingani and

colleagues included in their study.

Polypoidal Choroidal Vasculopathy

The link between CSCR and PCV has been well documented. The strikingly similar characteristics of the two diseases—namely increased choroidal permeability as seen with ICGA, increased choroidal thickness as demonstrated with EDI-OCT and histopathological findings of thin-walled choroidal vessels in PCV—support the theory that CSCR and PCV may be part of a pachychoroid-driven disease spectrum.[2]

Studies have suggested that PCV may be a manifestation of long-standing type 1 neovascularization. Samira Khan, MD, and colleagues showed that PCV can develop at the margins of long-standing Type 1 CNV in a variety of macular diseases.[12]

In another series of 27 eyes, Adrian Fung, MD, and colleagues showed that 36 percent of their patients with chronic CSCR and Type 1 neovascularization went on to develop PCV.[13] Reiterating the finding of increased choroidal permeability in PCV, researchers in Japan found that multifocal choroidal hyperfluorescence on ICGA occurs more frequently in patients with PCV than in those with AMD.[14]

Previous histological and imaging studies found that the neovascular complexes in PCV are situated between the RPE and Bruch's membrane.[15] This further supports the theory that PCV is not a primary choroidopathy, but rather a secondary neovasculopathy and a variant of Type 1 neovascularization. The presence of vessel hyalinization, which is characteristic of PCV, implies the chronicity of the neovascular complexes.[16] The chronicity of PCV vessels and the findings of increased choroidal thickness and permeability in PCV suggest links between chronic CSCR, PNV and PCV.

Causative Theories

In pachychoroid spectrum diseases, the spatial distribution of RPE changes, neurosensory retinal detachment and neovascularization seem to correlate with localized choroidal thickening, vessel dilation of areas of Haller's layer and thinning of the choriocapillaris and Sattler's layers.[5]

A study using SS-OCT and OCT-A showed that the location of pathologically dilated Haller's layer vessels correlated to zones of reduced choriocapillaris flow, which implies that inner-choroidal ischemia seems to be related to the pathogenesis of pachychoroid diseases.[17] On a different note, another group hypothesized that impeded choroidal vascular outflow due to a thickened sclera and increased scleral rigidity causes the pachychoroid spectrum diseases in part.[18]

Evidence of the role genetics plays in the development of pachychoroid-related diseases has been increasing. Mathieu

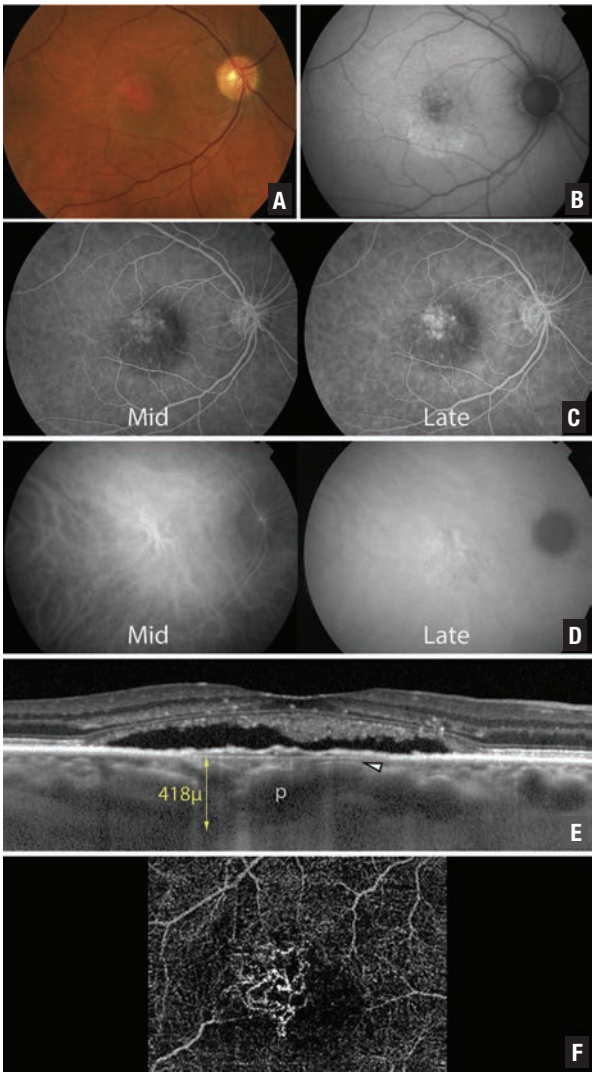

Figure 2. Multimodal imaging of the right eye of a 63-year-old female with pachychoroid neovasculopathy from Kunal Dansingani, MD, and colleagues.[11] Color photograph (A) and fundus autofluorescence of the right eye show non-specific retinal pigment epithelium changes with a dependent morphology. Mid-and late-phase fluorescein angiography (C) reveal an area of poorly defined hyperfluorescence with minimal late leakage. Indocyanine green angiography (D) shows large, dilated choroidal vessels (pachyvessels) with focal choroidal hyperpermeability, but a late-phase plaque is not definitely visible. Optical coherence tomography (E) shows subretinal fluid, subfoveal debris and pachyvessels (p) with overlying choriocapillaris thinning (white arrow) and a shallow, irregular PED. En-face OCT angiography (F) through the pigment epithelial detachment shows a tangled network of type 1 neovascular tissue. (*Used with permission. Dansingani KK, et al. Am J Ophthalmol. 2015;164:1243-1254 e2.*)

Lehmann, MD, and colleagues in France studied five CSCR patients and their relatives with enhanced depth OCT and found that 50 percent of the eyes from relatives had a thick choroid.[4] This observation suggests that the pachychoroid trait could potentially be a dominantly inherited condition, predisposing to CSCR depending on other exogenous or endogenous factors. Interestingly, a Japanese study also reported that the genetic background of patients with choroidal hyperpermeability and Type 1 neovascularization was different from those with AMD.[19]

Potential Therapeutic Options

Improved detection and recognition of the more severe manifestations of the pachychoroid disease spectrum has important treatment implications. Two treatment options have emerged: photodynamic therapy and anti-VEGF injections.

• ***PDT.*** As evident in the EVEREST II study, PDT has established itself as an important therapeutic consideration for PCV.[20] Additionally, sufficient evidence suggests that PDT may be a useful treatment option for chronic CSCR.[21] Because PNV exists on the spectrum of CSCR to PCV, PDT may be a viable therapeutic option for this disease as well.

• ***Anti-VEGF therapy.*** This treatment has to be considered when Type 1 neovascularization is present with pachychoroid related diseases. A group from Spain treated 18 consecutive unilateral PNV patients with anti-VEGF injections (ranibizumab [Lucentis, Roche/Genentech] or aflibercept [Eylea, Regeneron]) and found that choroidal thickness decreased significantly from baseline to month 12 in treated eyes.[22] The subfoveal choroidal thickness of treated eyes decreased from a mean of 318 µm at baseline to 267 µm at 12 months. Based on this finding, the authors hypothesized that anti-VEGF injections may reduce choroidal vascular permeability and, thus, decrease PNV activity.

Another group from Japan demonstrated that a treat-and-extend regimen of intravitreal aflibercept is effective in terms of vision improvement and resolution of exudative changes in both PNV and eyes with Type 1 neovascular AMD.[23] Interestingly, eyes with PNV required fewer injections, and among eyes with PNV, those with polypoidal lesions required fewer injections than those without polypoidal lesions.

Conclusion

PPE, CSCR and PCV fall within a spectrum of pachychoroid related disease that can result in RPE changes, branching vascular networks, Type 1 choroidal nevascularization (PNV) and PCV. Recognition and identification of the earlier stages of the disease spectrum could potentially avoid mismanagement or over-investigation. For the more advanced stages of the disease spectrum, therapies that target the pachychoroid aspect of the disease, such as PDT and anti-VEGF injections, could potentially help achieve long-term disease stability.

Dr. Mandelcorn is an associate professor of ophthalmology at the University of Toronto. Dr. Yap is a vitreoretinal fellow there.

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

Demystifying the Global Surgical Package

When you can and cannot bill for services during the 90-day surgical global period.

The question, "Can I bill for that service during the 90-day global period?" comes up periodically from clients. Often, the question is prompted because the patient requires services outside the typical postoperative care. That might include additional office visits and diagnostic tests. Some cases may require additional procedures, including intravitreal injections.

Medicare instituted a global surgery policy in 1992 as part of physician payment reform. Under this policy, Medicare pays a single fee for all necessary services normally furnished by the surgeon before, during and after the procedure. The policy describes services included in the national definition of "global surgery," as well as the services that are excluded and paid separately.

This article reviews the types of services included and excluded from the global payment for surgical procedures and provides examples of some of the more common areas of confusion.

Global Services Included

The Medicare Claims Processing Manual (MCPM) outlines the services included in and excluded from the global services package.[1] Major surgeries are defined as those procedures that have 90-day postoperative periods. The Medicare-approved amount for these procedures includes payment for the following services related to the surgery:

- Preoperative visits after the decision is made to operate, beginning with the day before surgery.
- Intraoperative services usual and necessary to the surgical procedure.
- Additional medical or surgical services required of the surgeon during the postoperative period to treat a complication, but that do not require a return to the operating room.
- Follow-up visits during the postoperative period related to recovery.
- Most surgical supplies (such as some injectable medications) unless identified as exclusions.

Global Services Excluded

Those services excluded from the global surgical package and reimbursed separately include:

- The initial evaluation by the surgeon to determine the need for surgery. If this service is provided during the global period, append the appropriate modifier to the office visit code to secure reimbursement.
- Services of other physicians (outside of a group practice), unless this is a shared-care surgery involving a transfer of care.
- Visits unrelated to the diagnosis for which the surgical procedure is performed. Modifier 24 identifies these visits as unrelated.
- Clearly distinct surgical procedures that are not reoperations or treatments for complications.
- Diagnostic tests.
- Treatments for postoperative complications that require a return trip to the operating room.
- Unplanned, medically necessary return trips to the OR for any reason and without regard to fault are separately reimbursed, but at a reduced rate. Under the modifier 78 rules, the payment for reoperations is the value of the intraoperative service for the CPT code. The postoperative clock does not restart from the date of the procedure.
- If a less-extensive procedure fails, and a more extensive procedure is required, the second procedure is payable separately.

Diagnostic Tests

The most frequent question we are asked is associated with diagnostic testing. The MCPM states that diagnostic tests are not part of the global surgical payment. When medically necessary, diagnostic testing is reimbursed during the postoperative period, no modifiers are required to facilitate payment.

The test needs to provide diagnostic value. For example, a physician documents postoperatively that a recent retinal-detachment surgery was successful and the retina is now flat. The surgeon draws the successful retinal-detachment repair and submits a claim for extended ophthalmoscopy (EO) (CPT 92226). Performing a test to document a successful outcome is not likely medically necessary.

National Government Services, a Medicare administrative contrac-

(Continued on page 50)

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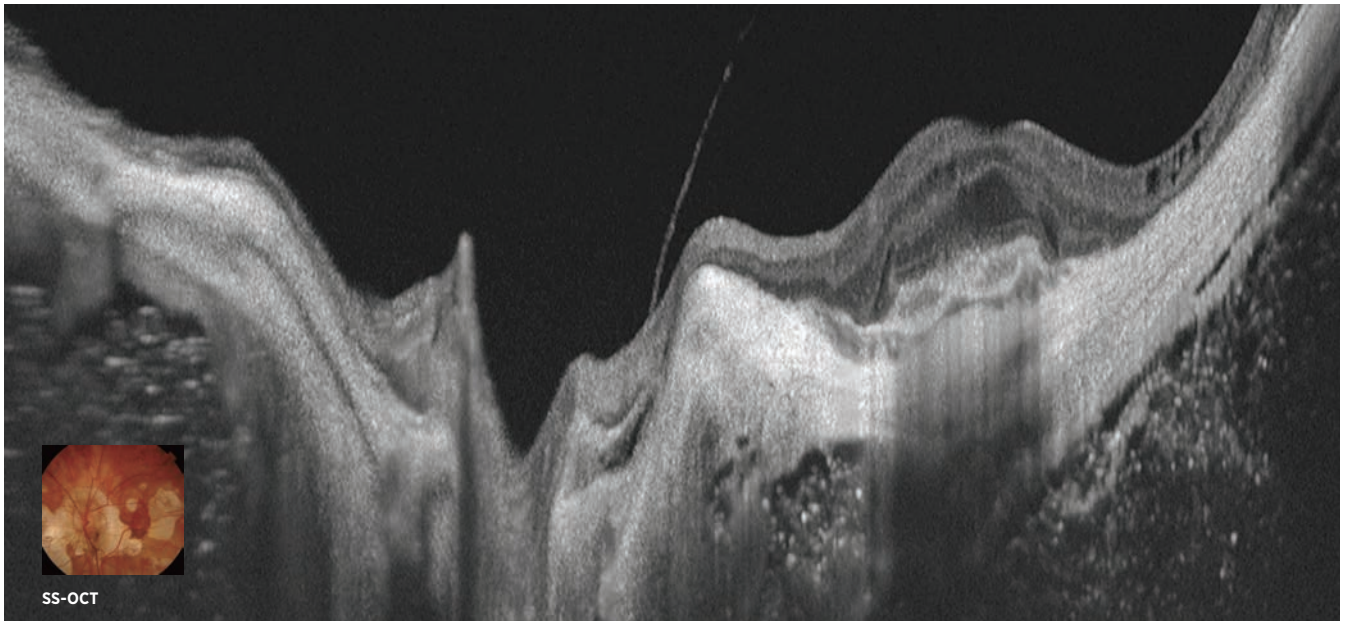

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tor for several states, published the local coverage determination L33567, Ophthalmology: Posterior Segment Imaging (Extended Ophthalmoscopy and Fundus Photography), which addresses billing an EO during the postoperative global period. It states:[2]

> *Extended ophthalmoscopy (codes 92225, 92226) performed during the global surgery period of an ophthalmologic surgery procedure, by the same provider performing the surgery, will not be separately payable unless unrelated to the condition for which the surgery was performed.*
>
> *Extended ophthalmoscopy is a physician service (examination of the eye) commonly occurring during the global postoperative period of ophthalmic surgery. As a physician service, it is included in the aftercare of the patient and is not separately billable.*

In contrast, if a vitrectomy to treat an unresolved vitreous hemorrhage from diabetic retinopathy is followed by an optical coherence tomography scan during the postoperative period to evaluate residual macular edema, the test is likely medically necessary.

In-office Procedures

An intravitreal injection is sometimes reimbursed during the global period. The reason for the injection is the key question to consider. For example, an injection in the exam lane to treat residual edema following an inner limiting membrane peel would be considered postoperative care. The injection is to treat a problem related to the ILM peel. Unless the injection was preplanned (staged) before the ILM peel, the procedure is not billable; the drug, however, is.

Group Practice Issues

In a multispecialty ophthalmic practice, sometimes the retina specialist is asked to address a complication from another surgeon. For example, six weeks following cataract surgery, your partner, Dr. Cataract, sends you a patient to evaluate for possible cystoid macular edema. Following an evaluation, OCT and an angiogram, you confirm CME in the operative eye. Unfortunately, since you and Dr. Cataract are partners in the same practice, the visit is postoperative care for a complication from the cataract surgery.

The MCPM includes a reference for physicians in group practice.[3] It states:

> *When different physicians in a group practice participate in the care of the patient, the group bills for the entire global package if the physicians reassign benefits to the group. The physician who performs the surgery is shown as the performing physician.*

Physicians of the same specialty in a group practice function collectively as the "surgeon" and should abide by the global surgery rules. In this context, an associate is not distinguished from the performing physician and inherits the limitations the global surgery policy imposes.

The office visit to evaluate a complication of cataract surgery by your partner is part of the global payment. Do not append modifier 24, calling this an unrelated office visit. The tests, which are not part of the global package, are separately reimbursed. As mentioned, injections in the exam lane to treat CME are postoperative care, but the drug is reimbursed.

Conclusion

Knowing which items and services are included in or excluded from the global package can be confusing. When deciding if a service is related to the surgery and, therefore, part of the postoperative care, consider whether the problem being addressed may have occurred regardless of the surgery. For instance, two months following an uncomplicated ILM peel, the patient has a retinal detachment in the same eye. Could the RD have occurred regardless of the ILM peel? If you answer a definitive "yes," then this is not likely a postoperative complication and the services to evaluate and treat the RD are likely unrelated to the ILM peel. Therefore, they are separately reimbursed.

For more information on reimbursement for surgical procedures during the postoperative period, see "Avoiding Post-Surgical Modifier Confusion" (September 2017).[4]

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By Richard Mark Kirkner »

Drilling Down Into Retina Robotic Surgery

Trial shows which steps take longer than manual surgery and the impact on involuntary hand movements.

Results from the first trial of robotic retina surgery in humans are in, and researchers at the at the University of Oxford in England have reported that membrane dissection takes about four times longer with the robotic device than manual surgery, and that the difference in the amounts of microtrauma between the two approaches were statistically insignificant, but the robot showed the potential to deliver other benefits in retinal microsurgery.[1] They reported their results in *Nature Biomedical Engineering*.

The trial utilized the robotic surgery platform that Preceyes BV of Eindhoven, the Netherlands, has been developing in collaboration with Oxford researchers. The researchers performed the trial at Oxford's John Radcliffe Hospital, involving six patients randomly assigned to robot-assisted surgery and six to standard manual surgery to dissect epiretinal membrane or inner limiting membrane.

In the second phase of the trial, the team used the robot to inject recombinant tissue plasminogen activator subretinally to displace hemorrhage under local anesthesia. In the ILM peels, all holes were closed; in the ERM dissections, all membranes were removed. All study subjects experienced an improvement in their vision as a result.

Breaking Down the Operation

'This is a huge leap forward for delicate and technically difficult surgery, which in time should significantly improve the quality and safety of this kind of operation," says Robert MacLaren, MB, ChB, DPhil, professor of ophthalmology at Oxford. "The trial also showed that the robot has great potential for extending the boundaries of what we can currently achieve."

While draping and installing the surgical robot did not disrupt the normal surgical work flow, the average time of the operation—between inserting the first trocar to injecting the subconjunctival antibiotic prior to removing the lid speculum—was 31 minutes for the manual group and 44 minutes for the robot group ($p<0.0001$).

Specific steps of the operation also took longer with the robot. Moving a pick from the anterior vitreous cavity to a position over the macula where it's safely poised to engage the membrane took 2 minutes, 22 seconds vs. 12 seconds ($p=0.002$). Raising the flap of either the ILM or ERM with the pick took 4 minutes, 55 seconds vs. 1 minute, 20 seconds.

The study showed the robot can overcome involuntary movements of the surgeon's hand. The authors noted, "For instance, while the surgeon routinely needs to engage a needle tip or pair of forceps within the thin (<20 µm) inner limiting membrane of the retina without damaging deeper structures, human physiological tremor is present in the order of 100 µm when transmitted to the instrument tip." Eliminating those micromovements as a factor could enable new intraocular procedures that require "supra-human levels of precision," the study authors noted.

Robert MacLaren, MB, ChB, DPhil, at the console of the retina surgical robot. ***(Photo Courtesy University of Oxford)***

Report Due at AAO

Matteo Cereda, MD, a retinal surgeon at Sacco Hospital Eye Clinic in Milan, will report on the robotic platform at the American Academy of Ophthalmology next month in Chicago. Dr. Cereda conducted a feasibility study of the robot's integrated distance sensor.

Preceyes is also investigating the use of a virtual-reality simulator with the surgical robot as a training tool, and next year the Oxford investigators expect to start a trial using the robotic platform to deliver gene therapy to the retina with a higher degree of precision and less trauma than manual surgery.

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A Deeper Dive Into Abicipar Trials

Answers about vision outcomes, inflammation and where it fits in the treatment armamentarium. ***By Richard Mark Kirkner***

With the release of topline results from the Phase III SEQUOIA and CEDAR trials of abicipar pegol just before the annual meeting of the American Society of Retina Specialists, Allergan and its collaborative partner, Molecular Partners, touted that the investigational agent showed noninferiority to ranibizumab (Lucentis, Roche/Genentech) for treatment of neovascular age-related macular degeneration. However, some clinicians expressed concerns about the relatively high rates of inflammation reported in the abicipar treatment arms.

After 12 months of treatment, in both studies abicipar demonstrated similar efficacy after six or eight injections compared to 13 ranibizumab injections, and the overall rates of adverse events were similar among the three treatment arms.

In SEQUOIA, the proportion of patients with stable vision were 94.8 percent in the abicipar eight-week dosing arm; 91.3 percent in the abicipar 12-week arm; and 96 percent in the ranibizumab four-week arm. Treatment-emergent adverse event rates were 78.3 percent, 78 percent and 74 percent, respectively, across the three treatment arms.

In CEDAR, the proportion of patients with stable vision in the abicipar arms were 91.7 percent (eight-week dosing) and 91.2 percent (12-week dosing) vs. 95.5 percent for ranibizumab dosed every four weeks. Rates of treatment-emergent adverse events were 73.7 percent, 81.1 percent and 73.2 percent, respectively, across the treatment arms.

However, the rates of intraocular inflammation events were significantly higher in the abicipar groups in both trials. In SEQUOIA, 15.7 percent and 15.3 percent of patients in the abicipar eight- and 12-week arms reported inflammation vs. 0.6 percent in the ranibizumab arm. In CEDAR, those rates were 15.1 percent and 15.4 percent in the abicipar eight- and 12-week arms and 0 percent in the ranibizumab arms.

Allergan's official statement said the investigators are further analyzing these results as both trials continue on a masked basis for a second year. David Nicholson, PhD, Allergan's chief officer for research and development, told analysts the company is addressing the inflammation concerns by modifying the formulation of abicipar. The reformulated agent will be the subject of the upcoming MAPLE trial.

Here, investigator Raj Maturi, MD, of Midwest Eye Institute and associate professor at Indiana University School of Medicine in Indianapolis, answers questions about SEQUOIA and CEDAR.

Q What is the key findings of both the SEQUOIA and CEDAR trials?

A The trials showed non-inferiority of abicipar at a fixed 12-week regimen. The studies also disclosed that 91 percent of patients on a fixed 12-week regimen maintained or improved vision. Clearly there are other important points that a retina specialist would look for, including change in visual acuity from baseline as well as proportion with 2- and 3-line improvements. I suspect that these results are anticipated to be presented at a major meeting in the near future.

Q What about the design of SEQUOIA and CEDAR that makes the findings credible?

A These two trials involved a fixed-dosing regimen without any individual alteration of the regimen based on individual responses. There were no subgroups that received treatment at different intervals based on individual response.

Q What was the dosing regimen?

A In both studies, there were three arms: abicipar Q8 weeks; abicipar Q12 weeks; and the control, ranibizumab Q4 weeks. The Q8-week arm received three monthly doses followed by the eight-week treatment interval, while the Q12 arm received only two monthly doses followed by Q12-week dosing.

Q What do these trials reveal about the potential advantage of abicipar vs. existing intravitreal treatments for nAMD?

A Having a dependable drug that is able to last for almost 12 weeks would be a relative advantage for this disease. The treatment burden for patients would be reduced markedly.

Q Where would abicipar fit in the retina specialists' tool box—alongside existing therapies (and brolucizumab) or in place of

them? Or for refractory cases?

A A full evaluation of the results of both brolucizumab (Novartis) and abicipar would be necessary to make this judgment. A longer duration of action would generally imply one or more of the following: better drug affinity to vascular endothelial growth factor molecules; slower clearance from the retina/subretinal space; or slower breakdown of active components. Longer duration drugs could thus be considered more powerful.

For larger pigment epithelial detachments and more difficult-to-treat AMD lesions, I typically use aflibercept (Eylea, Regeneron). One of the longer-duration drugs would likely replace aflibercept in the near future.

For the less-active and responsive lesions, my first line choice continues to be bevacizumab (Avastin, Roche/Genentech). However, given a longer duration-of-drug effect, some patients may wish for one of these alternatives.

Q There has been a lot of concern over the inflammation outcomes in the trials. How should clinicians interpret these findings?

A The two Phase III studies were conducted with a biological agent that has since been improved. Allergan is conducting a smaller study, MAPLE, with this improved drug product. Biologicals are generally produced using genetically modified bacteria. Companies typically improve the purification process as they gain experience with this delicate extraction.

Q Drilling down into the inflammation issue, did that have any impact on functional vision in study subjects?

A Allergan has reported that inflammation rates were around 15 percent for both abicipar arms. The full dataset on inflammation-related visual loss has not been disclosed. I would anticipate that this would be presented at a future meeting or formal scientific publication.

Q What is the next step in the evaluation and development of abicipar?

A The company has stated that it wishes to file a Biologics License Application within the next six to nine months. Having dosed this drug in my patients over the last few years in multiple trials, I look forward to using this drug in my clinic in the very near future. RS

RETINA CALENDAR

OCTOBER

25
OPHTHALMOLOGY INNOVATION SUMMIT
OIS@AAO 2018
MARRIOTT MARQUIS, CHICAGO
Website: https://ois.net/ois-aao-2018/

26, 27
RETINA SUBSPECIALTY DAY
27-30
AAO 2018
AMERICAN ACADEMY OF OPHTHALMOLOGY ANNUAL MEETING
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2019

FEBRUARY 9

ANGIOGENESIS, EXUDATION, AND DEGENERATION 2019
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MANDARIN ORIENTAL MIAMI
Website: https://umiamihealth.org/bascom-palmer-eye-institute/healthcare-professionals/continuing-medical-education/upcoming-events

MARCH

1-2
EUROPEAN SOCIETY OF RETINA SPECIALISTS
NINTH EURETINA WINTER MEETING
PRAGUE
Website: http://www.euretina.org/euretina-9th-winter-meeting-prague-2019/

21-24
RETINA WORLD CONGRESS
FT. LAUDERDALE, FLA.
MARRIOTT HARBOR BEACH HOTEL
Website: https://www.healio.com/meeting/retinaworldcongress/home

30-31
21ST ANNUAL BUSINESS OF RETINA MEETING
AMERICAN SOCIETY OF RETINA SPECIALISTS
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APRIL

4-6
VIT-BUCKLE SOCIETY MEETING
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28 – MAY 2
ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY
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JULY

26-31
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EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR) in Patients with DME

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

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

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

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

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

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
Regeneron Pharmaceuticals, Inc.
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Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

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POWER TO PREVAIL

As demonstrated in phase 3 clinical trials evaluating BCVA,* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS† in DR in Patients with DME,[1] as well as your clinical experience

Start with EYLEA for proven efficacy outcomes[1]

AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema;
DR = Diabetic Retinopathy; RVO = Retinal Vein Occlusion.

Dosing driving efficacy outcomes across all indications.[1]
Learn more at EYLEA.us/dose

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

Please see adjacent Brief Summary.

*Best-corrected visual acuity.
†Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

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