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GA in the Primary Eye Care Clinic: Improving Detection, Understanding Therapy, and Perfecting the Referral

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GA in the Primary Eye Care Clinic: Improving Detection, Understanding Therapy, and Perfecting the Referral

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Content Source

This continuing education (CE) activity captures content from a synchronous in-person symposium.

Activity Description

This supplement summarizes a discussion on geographic atrophy, including risk factors, the complement system, treatments, and the pipeline.

Target Audience

This certified CE activity is designed for optometrists.

Learning Objectives

Upon completion of this activity, the participant should be able to:

- **Summarize** epidemiologic data about AMD and GA, and **identify** risk factors for AMD and GA
- **Identify** the deleterious effects of AMD and GA on overall patient health, quality of life, and the health care system
- **Explain** the connection between the development of GA and the complement system
- **Compare** how various imaging modalities used in GA diagnosis depict disease
- **Understand** the current state of the GA therapeutic pipeline
- **Anticipate** how possible changes to GA treatment strategies will affect referral patterns and **recognize** ways to improve collaborative care models to ensure high-quality patient care is delivered

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for credit.

1. Please rate your confidence in your ability to detect geographic atrophy (GA) and refer these patients to a retina specialist (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. An 82-year-old man presents with a chief complaint of visual disturbance in his right eye. He is a smoker with a past medical history significant for hypertension, heart disease, and hyperlipidemia. He is African American. You note pigmentary abnormalities in both eyes (right eye>left) as well as numerous large drusen. All of the following represent this patient's risk factors for age-related macular degeneration (AMD) EXCEPT:

a. Older age
b. Smoking status
c. African American race
d. Hyperlipidemia

3. All of the following represent the deleterious effects of AMD and GA on patient's quality of life EXCEPT:

a. Increased time spent reading
b. Less engagement with friends
c. Need for visual aids
d. Less exercise

4. Which one of the following statements is hypothesized to be involved in the pathophysiology for GA?

a. Complement deposition at the level of the inner nuclear layer
b. Increased regulation of the complement system
c. Blood-retina barrier activation
d. Continuous low-grade complement-mediated inflammation

5. You are evaluating a 76-year-old woman with AMD. Her color fundus photo shows a distinctly demarcated area of hypopigmentation with increased visibility of choroidal vessels in her right eye, consistent with GA. Her left eye does not show any signs of GA. Which imaging modality may help you identify incomplete retinal pigment epithelial and outer retinal atrophy (iRORA), pigment epithelial detachment, and complete retinal pigment epithelial and outer retinal atrophy (cRORA) to determine this patient's likelihood of developing GA in her left eye?

a. Color fundus photography
b. Optical coherence tomography (OCT)
c. B-scan ultrasonography
d. Fluorescein angiography

6. An 85-year-old woman presents for evaluation. She has advanced GA in her left eye with hand motion vision. Her right eye has foveal-sparing GA, with a VA of 20/30. OCT imaging shows no signs of exudation in her right eye. Which of the following is the next best step in management of this patient?

a. Observation
b. Initiation of anti-VEGF therapy in her right eye
c. Initiation of complement-inhibition therapy for GA in her right eye
d. Initiation of intravitreal steroid therapy in her right eye

7. A 76-year-old woman presents for evaluation. She has bilateral extrafoveal GA that has progressed significantly over time. She is otherwise healthy and motivated to keep her eyesight. Which of the following is NOT a recommended next step for this patient?

a. Referral to a retina specialist
b. Observation at this time
c. Provide Amsler grid and AREDS
d. Advise therapy with omega-3

8. What is responsible for approximately 90% of central vision loss globally?

a. Exudative AMD
b. Cataract
c. Diabetic retinopathy
d. Retinal vascular occlusion

9. An 87-year-old Caucasian man who smokes presents for examination. He notes blurry vision in both eyes. You note diffuse punctate epitheliopathy, 1+ nuclear sclerotic cataracts, and numerous moderately sized drusen. OCT imaging reveals no signs of exudation. Which is the most important next step in management of this patient?

a. Discussion of smoking cessation
b. Cataract evaluation
c. Lifitegrast prescription
d. Brimonidine prescription

10. A 76-year-old Caucasian woman with bilateral GA presents for evaluation. She is noting increasing difficulty with reading and starting to feel disengaged from social activities. On imaging, you note her GA is extrafoveal and multifocal. Which of the following statements about her likely progression is TRUE?

a. Her GA is not likely to progress because it is extrafoveal
b. Her GA is likely to progress because it is extrafoveal and multifocal
c. Her GA is not likely to progress because it is multifocal
d. There is insufficient data given to determine if her GA is likely to progress

11. According to studies, what percentage of patients with GA who have a driver's license report not feeling confident driving during the day?

a. 25%
b. 52%
c. 75%
d. 100%

12. Genetic defects in the complement cascade accounts for what percentage of AMD heritability?

a. 10% to 20%
b. 30% to 50%
c. 40% to 60%
d. 70% to 90%

13. You are examining a 72-year-old patient with a history of AMD. Which of the following imaging modalities would most help you identify reticular pseudodrusen to determine this patient's risk profile for developing GA?

a. Color fundus photography
b. OCT
c. Fluorescein angiography
d. B-scan ultrasonography

14. You are examining an 84-year-old patient with a history of AMD with GA. He is noting increasing difficulty with his activities of daily living and is no longer able to drive. Which of the following imaging modalities can help quantify his GA into a pattern that might confer higher risk of progression, such as diffuse-trickling?

a. Color fundus photography
b. OCT
c. Fundus autofluorescence
d. B-scan ultrasonography

15. You are evaluating a 75-year-old patient with GA. She notes progressive decline in her vision during the past year, including increasing difficulty driving.You start her on pegcetacoplan monthly. What is the target molecule of this drug?

a. C3
b. C4
c. C5
d. C6

16. You are evaluating an 80-year-old patient with GA who is currently undergoing intravitreal therapy with pegcetacoplan for his GA. Which of the following statements is TRUE regarding ongoing monitoring of this patient?

a. Encourage self-monitoring and perform in clinic monitoring to check for exudative conversion
b. This patient must be screened for neovascular glaucoma every other month
c. This patient must be screened monthly for choroidal melanoma
d. This patient must be started on an IOP-lowering prophylaxis

Geographic Atrophy in the Primary Eye Care Clinic: Improving Detection, Understanding Therapy, and Perfecting the Referral

AMD and GA: Epidemiology, Risk Factors, and Natural History

CAROLYN E. MAJCHER, OD, FAAO, FORS

Advanced age-related macular degeneration (AMD) is subtyped into neovascular AMD (also called exudative or wet AMD) and geographic atrophy (GA); it should be noted that these two advanced forms of AMD are not mutually exclusive, and patients have been known to present with both subtypes in the same eye. Early and intermediate AMD is collectively termed dry AMD.

The prevalence of all AMD types is estimated to be 11 million in the United States and 170 million worldwide[1]; in the United States, the prevalence of all AMD is estimated to reach 22 million by 2050.[2] Approximately 85% to 90% of patients with AMD have nonexudative disease[3]; by 2050, as many of 19.8 million patients in the United States may have nonexudative AMD.

Regarding GA, in particular, prevalence has grown. The estimated prevalence of GA was 1.75 million in 2004 and nearly 3 million in 2020.[4] The percentage of the population with GA grows with age, with one study finding GA in 1.29% of patients 65 to 69 years old and in 11.96% of patients 85 to 90 years old.[5]

Until the recent approval of therapies for GA, many optometrists have been focused on identifying exudative AMD—and for good reason, as this condition is responsible for approximately 90% of central vision loss globally.[6] Just as our field has been tasked with identifying exudative AMD as early in possible and promptly referring to a provider authorized to administer anti-VEGF therapy, so too must optometrists now identify GA in its earliest stages and refer promptly to a retina specialist. Although many providers are excited by new GA therapies and the prospects of directing patients with GA to providers, we cannot take our eye off the ball when it comes to our obligations regarding catching exudative AMD conversion.

In GA, the photoreceptors, retinal pigment epithelium (RPE), and the choriocapillaris are thinned or, in advanced cases, completely lost. Coleman et al described GA as "a discrete area of retinal depigmentation at least 175 µm in diameter with a sharp border and visible choroidal vessels in the absence of [wet] AMD in the same eye."[7] Vision loss associated with this condition is irreversible; and, unlike wet AMD, vision cannot be improved or restored with current GA therapeutic options. Intervention may result in significantly slowed rates of GA lesion growth, and earlier intervention may result in lower rates of visual compromise.

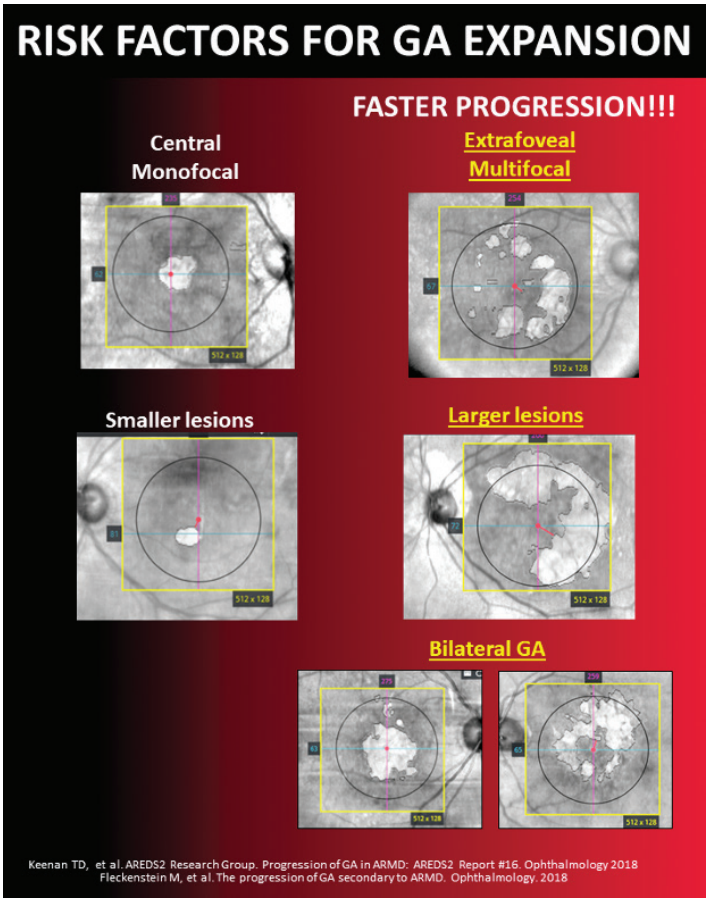

Image courtesy of Carolyn E. Majcher, OD, FAAO, FORS

Figure. Lesions that are multifocal, extrafoveal, and larger are at risk for rapid GA progression relative to unifocal, center-involving, and small lesions. Bilateral status is also linked with rapid GA progression.

Risk factors for AMD of any type include a number of nonmodifiable risk factors, such as advanced age, white race, and genotype.[8-11] In particular, the presence of risk alleles CFH and ARMS2 have been linked with increased risk of AMD progression,[8] and the CFH variant Y402H is linked with increased risk for GA development.[12]

Smoking is the leading modifiable risk factor for developing AMD.[8] Regarding GA, in particular, smoking increases the likelihood of developing GA by a factor of 3.5 if a patient has a smoking history of 40 pack years.[9] Other modifiable risk factors for AMD development include obesity, hypertension, and Western diets.[13,14]

Clinical biomarkers offer practical predictors of GA progression. Extrafoveal (also called noncenter-involving) lesions tend to progress faster than center-involving lesions, multifocal lesions (ie, noncontiguous lesion clusters) progress faster than unifocal lesions, large lesions progress faster than small lesions, and bilateral GA status is linked with faster lesion growth (Figure).[15-17]

GA is often described as a condition that progresses slowly—that does not mean, however, that primary eye care providers should refrain from careful detection and prompt referral, as timely intervention could be key to preserving vision for some patients. Data from the second Age-Related Eye Disease Study (AREDS2) show that patients with extrafoveal GA lesions show evidence of central involvement within 2.5 years, and the 4-year risk of moving from extrafoveal regionality to center involvement was 57%.[15]

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Burden of AMD and GA, and the Role of the Complement System

MARK T. DUNBAR, OD, FAAO

The burden of illness for patients with age-related macular degeneration (AMD) and geographic atrophy (GA) is not limited merely to reduced visual acuity. The downstream effects of visual disruption due to AMD and GA include difficulty with household chores and personal hygiene, reduced driving confidence, lower rates of physical activity, and overall deterioration of mental health—all of which leads to increased social isolation. These reductions in quality of life (QoL) are often significant.

In 2020, Patel et al found that patients with GA had worse QoL scores and visual function compared with age-matched controls.[1] Patients with GA performed worse during near activities, distance activities, and peripheral vision testing, and had lower scores in assessments linked to mental health, driving, and social functioning.[1] These observations buttressed those made by Orr in 2016, who also found that GA was linked with reduced functioning with near and distance activities as well as a reduction in understanding activity limitations.[2]

Patients with GA report higher rates of deteriorating vision each year compared with control patients (82% versus 25%, $P < .05$).[1] Driving, a key component of independence for the aging community, is affected by GA. Among GA patients with driver's licenses, 52% lack confidence with daytime driving and 88% lack confidence when driving at night (Figure 1).[1] This discomfort with nighttime driving may be linked to delayed dark adaptation, a consequence of advancing AMD. A 2018 study in the United Kingdom found that two-thirds of patients with GA were determined to be ineligible to drive within median 1.6 years of GA diagnosis, and that approximately one in six patients with

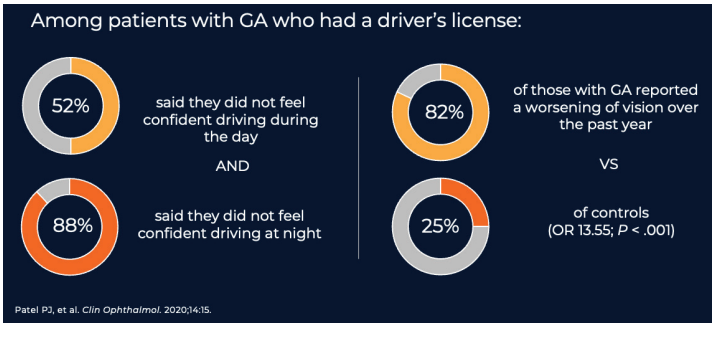

Figure 1. A majority of patients with GA do not feel comfortable driving during the day and a vast majority of them do not feel comfortable driving at night. Further, 82% of patients with GA reported worsening vision over the past year compared with only a quarter of control patients, a difference that was statistically significant.

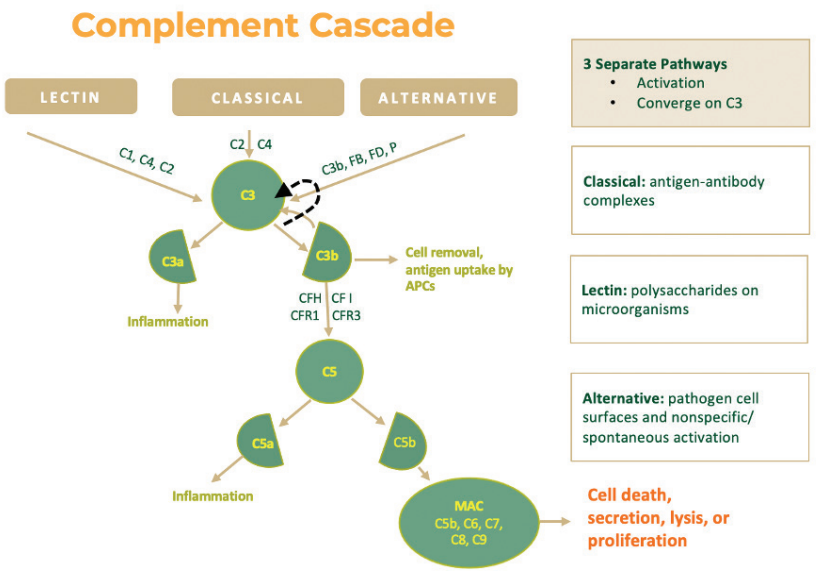

Figure 2. This simplified schematic of the complement cascade illustrates how each of the three activation pathways in the complement system converge at C3 and again at C5. The formation of MAC, which is the terminus of the complement cascade, results in cell death. Adapted from Ricklin D, et al. *Immunol Rev.* 2016;274(1):33-58.

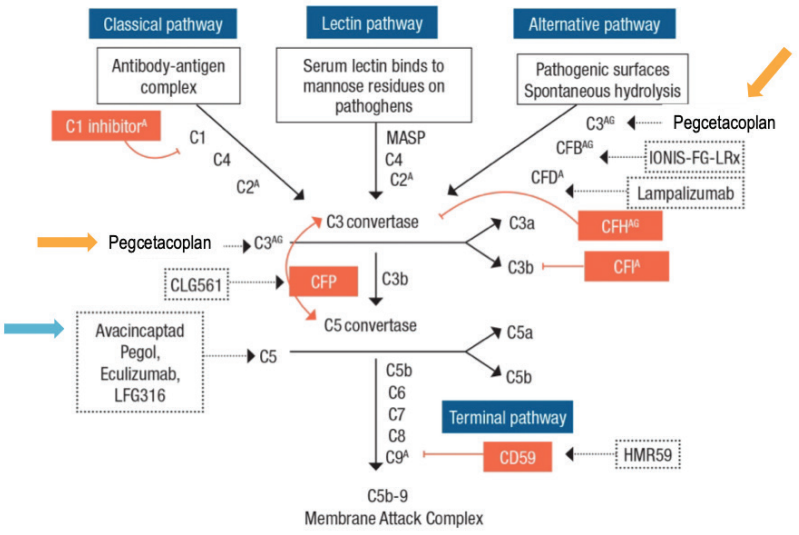

Figure 3. This more detailed depiction of the complement cascade indicates the targets of various approved, failed, and investigational drugs. The approved drugs pegcetacoplan and avacincaptad pegol target C3 and C5, respectively. Adapted from Warwick A, et al. *J Clin Med.* 2014;3:1234-57. http://creativecommons.org/licenses/by/4.0/

GA were eventually diagnosed as legally blind.[3] If primary eye care providers can quickly identify GA and refer to a provider authorized to administer care, then we may be able to prevent loss of independence among some patients with GA.

Although the pathophysiology of GA is not entirely understood, it is believed that oxidative stressors from sources such as light, oxygen, lipids, and retinoids combine with the aforementioned modifiable (eg, smoking, diet) and nonmodifiable (eg, genotype) risk factors to result in deposits in the Bruch membrane/retinal pigment epithelium/choroid complex, resulting in a breakdown of the blood-retina barrier and continuous low-grade, complement-mediated inflammation.[4,5] Regarding genotype, current evidence suggests that the presence of gene CFH is one of the (if not *the*) leading genetic determinate in developing AMD, and may be responsible for up to 40% to 60% of AMD inheritance.[6]

Drusen deposits are a hallmark sign of AMD. In patients with GA, drusen deposits have been shown to contain complement components C1q, C3, C5, and C3b-9, suggesting that dysregulation of the complement system may be at play in the pathogenesis of GA.[4] The complement system, which is part of the innate immune system, helps protect the body from foreign pathogens (Figure 2). The three pathways to activating the complement system are the classical, the alternative, and lectin pathways. They converge at C3 and, further downstream, at C5. The ultimate product of complement system activation is the formation of membrane attack complex (MAC), which leads to cell death (and, in the case of GA, retinal cell death).[7]

Overactivation of the complement system may be key to driving GA genesis and progression. Two drugs approved by the FDA for the treatment of GA target the complement system. They are the C3-inhibitor pegcetacoplan and the C5-inhibitor avacincaptad pegol. Figure 3 depicts the complement targets of these drugs, as well as the targets of failed and investigational drugs. Patients who are referred to a retina specialist by their primary eye care provider may be considered for either of these approved treatment options if the retina specialists determines that they are a suitable candidate for therapy.

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Imaging AMD and GA

MOHAMMAD R. RAFIEETARY, OD, FAAO, FORS, ABO

Diagnosis of geographic atrophy (GA) is primarily done via imaging. The modalities with the most clinical utility for characterizing and diagnosing GA are color fundus photography (CFP), optical coherence tomography (OCT), and fundus autofluorescence (FAF). Each modality has its own drawbacks and benefits. Although researchers have concluded that it may be a best practice to use multimodal imaging for the detection of GA[1], this guidance ignores real-world limitations. The practical applications of these modalities will differ among primary eye care clinics based on access to technology and clinical workflow preferences.

COLOR FUNDUS PHOTOGRAPHY

Many optometrists have access to CFP in their clinics. It has been used extensively in natural history studies of GA, and has been described as a good tool for measuring GA lesion area by Kanifar et al[1], and can be used to assess whether lesions are foveal or extrafoveal, which progress faster.[2] CFP may be a vital tool in detecting otherwise undetected age-related macular degeneration (AMD). Neeley et al found that, among eyes otherwise deemed normal after dilated eye examination by a primary eye care provider, approximately 25% showed evidence of AMD on CFP when reviewed by trained raters.[3] Among eyes that were undiagnosed with AMD in that study, approximately 30% had large drusen.[3] Per these data, primary eye care providers may benefit from adding CFP to slit lamp examinations.

The earliest stages of AMD may not manifest on CFP, allowing some eye care providers to overlook nascent disease (Figure 1). However, in many cases, intermediate and advanced AMD are clearly depicted on CFP, and choroidal tissue will be observed. Use of another modality may be warranted in some patients whose CFP images do not match patient-reported symptoms of visual disruption.

Figure 1. CFP may fail to adequately illustrate nascent AMD in some patients, but it depicts intermediate and advanced disease clearly in some patients.

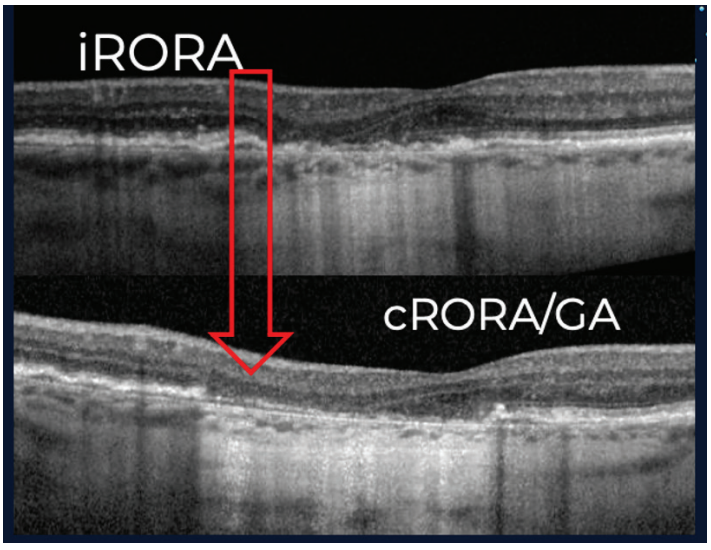

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Figure 2. Progression from iRORA to cRORA is depicted in these two OCT B-scans. Increased choroidal hypertransmission in the cRORA patient indicate that atrophy has significantly advanced.

OPTICAL COHERENCE TOMOGRAPHY

In the literature, use of en face OCT images has been used to predict progression of GA,[4] and B-scan images have been used to classify levels of atrophy.[5] Primary eye care providers may find OCT a useful modality for imaging. Indeed, a 2020 study by Midena et al found that OCT imaging provided gradable images in almost all instances and allowed better detection of AMD than CFP.[6]

On B-scan, areas of choroidal hypertransmission indicate increased GA activity, and separation of the retinal pigment epithelium (RPE) and Bruch membrane is also depicted.[7] The Classification of Atrophy Meeting (CAM) Group categorized atrophy as seen on OCT as either incomplete RPE and outer retinal atrophy (iRORA) or complete RPE and outer retinal atrophy (cRORA).[5] While these distinctions might have limited utility in clinical settings, they nevertheless illustrate the progressive nature of GA as seen on imaging (Figure 2).

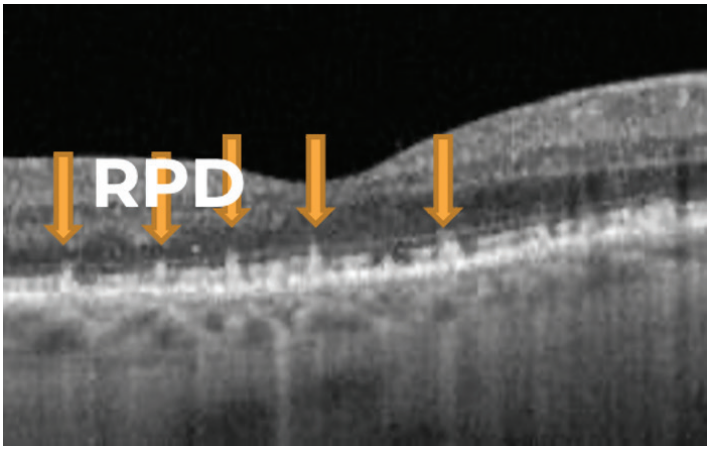
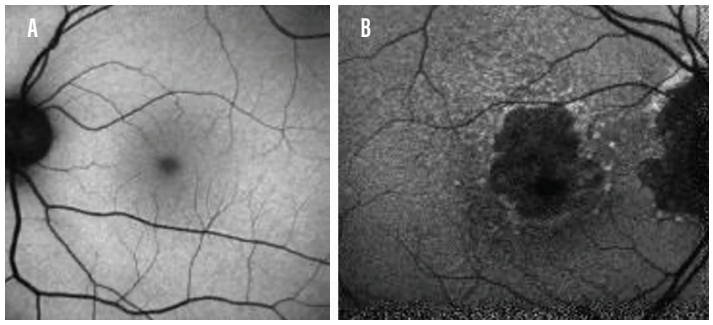


Image courtesy of Mohammad R. Rafieetary, OD, FAAO, FORS, ABO

Figure 3. RPD as seen on OCT. Patients with RPD may be at particularly high risk for developing GA.



Images courtesy of Mohammad R. Rafieetary, OD, FAAO, FORS, ABO

Figure 4. A healthy retina as depicted on FAF (A). A large, unifocal lesion is observed on FAF in a GA patient (B).

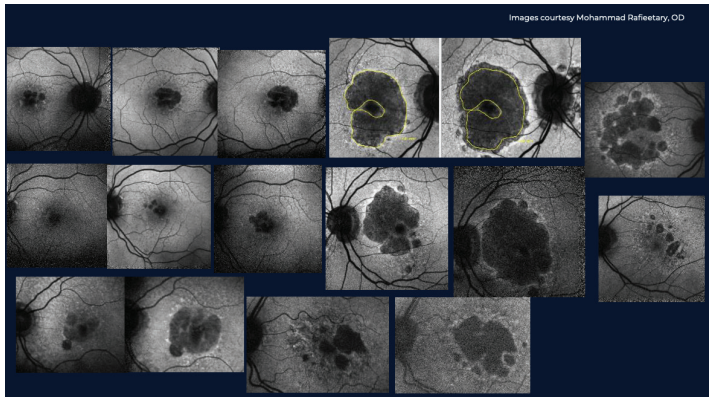


Figure 5. Clinicians using FAF may wish to categorize lesions based on size, configuration, location, or fluorescence pattern if they wish to prognosticate the rate of GA progression.

Reticular pseudodrusen (RPD), which poke up through the ellipsoid zone and the external limiting membrane, may also be depicted on OCT (Figure 3). The presence of RPD has been linked with a 4.9-fold higher risk of GA progression,[8] and is considered "an early manifestation of the process leading to GA."[9]

FUNDUS AUTOFLUORESCENCE

In 2011, FAF was described in the literature as the gold standard for evaluating progressive GA enlargement," and researchers in several pivotal studies have used FAF as the modality for imaging lesion growth.[10] This noninvasive modality can clearly depict lesions in an *en face* fashion (Figure 4). Lesions on FAF can be categorized based on size, configuration, location, and fluorescence pattern, which in turn can be used to predict progression (Figure 5). For example, eyes with banded and diffuse fluorescence patterns have been shown to progress faster than eyes with focal FAF patterns,[11] and multifocal lesions progress faster than unifocal lesions.[12]

The modality (or modalities) you use in your primary eye care clinic will depend on personal preference and access to technology. Regardless of which modality primary eye care providers use to image AMD and GA, they should know that prompt referral and thorough documentation are the first steps to getting patients into the care of a provider who can administer therapy.

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FDA-Approved Treatments for Geographic Atrophy

CAROLYN E. MAJCHER, OD, FAAO, FORS

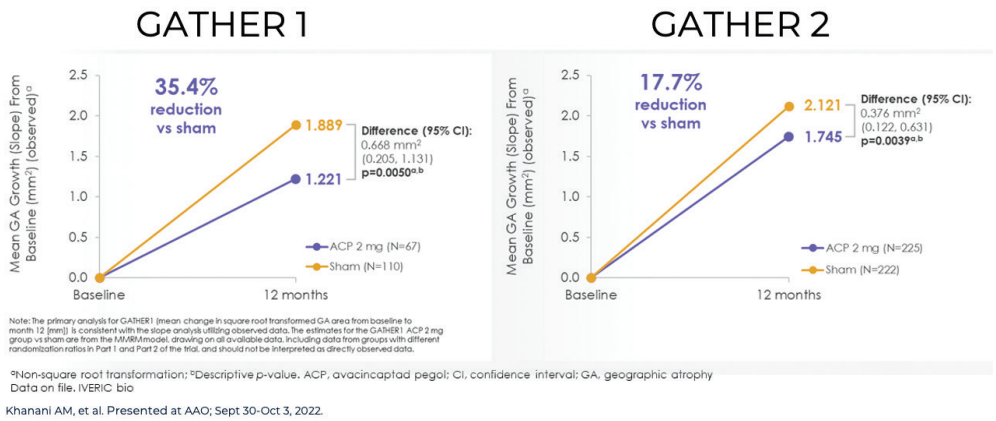
The C3-inhibitor pegcetacoplan and the C5-inhibitor avacincaptad pegol are approved by the FDA for the treatment of geographic atrophy (GA). Both are delivered via intravitreal injection. The safety and efficacy of each drug were assessed in pivotal studies, with the DERBY and OAKS studies assessing pegcetacoplan and the GATHER1 and GATHER2 studies assessing avacincaptad pegol.

Each set of studies used fundus autofluorescence (FAF) to assess the change in rate of lesion growth. One important difference between these studies were the inclusion/exclusion criteria. In DERBY/OAKS, patients with and without subfoveal GA were enrolled, and choroidal neovascularization (CNV) in the fellow eye did not exclude the patient from participation.[1] In GATHER1/2, only patients with nonfoveal GA were included, and patients were excluded if fellow-eye CNV was present.[2]

PIVOTAL STUDY DATA FOR AVACINCAPTAD PEGOL

GATHER1 was a pivotal phase 2b/3 trial in which patients were dosed with monthly 2-mg or 4-mg avacincaptad pegol or sham.[3] At month 12, the low-dose group experienced a reduction in GA growth of 27.4%; for the high-dose group, this reduction was 27.8%. Both rates were statistically significant.[3]

In GATHER2, which was a randomized, double-masked, sham-controlled, multicenter clinical trial, patients were randomly assigned to 2-mg treatment or sham for the first year of the study, and were thereafter randomly assigned to monthly or every-other-month (EOM) therapy until month 23, with a final



Khanani AM, et al. Presented at AAO; Sept 30-Oct 3, 2022.

Figure 1. Mean rates of observed GA growth in GATHER1 and GATHER2 were statically significant for the 2-mg treatment arms at month 12.

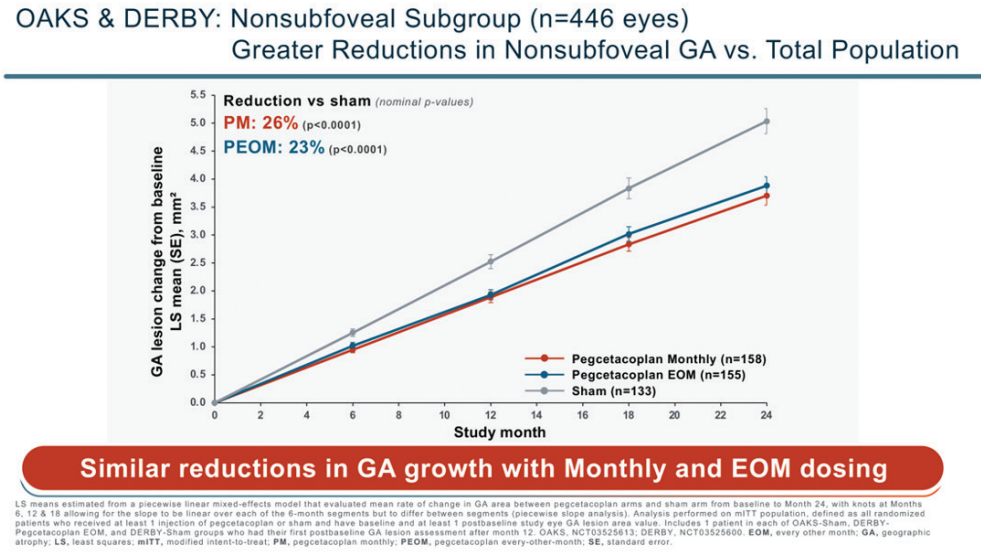


Figure 2. Reductions in GA lesion growth rate were significantly higher in patients with nonsubfoveal lesions compared with the total population in DERBY and OAKS at 24 months.

readout occurring at month 24.[3] The primary endpoint for the study, which was mean rate of growth (slope) in GA area over 12 months using square root transformation, was met.[3]

The mean rates of observed GA growth from baseline to 12 months in GATHER1 and GATHER2 showed, respectively, that treatment with the 2-mg dose resulted in a 35.4% reduction and a 17.7% reduction (Figure 1).[5] Both rates were statistically significant compared with sham.

PIVOTAL STUDY DATA FOR PEGCETACOPLAN

The DERBY and OAKS studies, which enrolled 621 and 638 patients, respectively, were a pair of phase 3, randomized, double-masked, sham-controlled studies with a primary endpoint of change in total area of GA lesions based on FAF at month 12.[1] Patients were randomly assigned to monthly or EOM treatment or sham and were observed for 24 months.

OAKS met the 12-month primary endpoint, and DERBY did not.[1] A prespecified pooled analysis of the combined DERBY and OAKS data showed that treatment resulted in a reduction in GA lesion growth rate of 17% in the monthly arm and 14% in the EOM arm.[6]

Patient outcomes were assessed again at month 18 and 24.[7,8] At 18 months, patients in the monthly and EOM arms in both individual studies experienced statistically significant reductions in lesion growth rates compared with sham. An assessment of pooled data found reduction rates of 17% and 15% in monthly and EOM arms, respectively.[7] At 24 months, growth reduction rates increased in both treatment arms in each study, again resulting in statistically significant rate reductions. The monthly and EOM arms in DERBY showed reductions in GA lesion growth of 19% and 16% compared with sham, respectively; in OAKS, those reductions were 22% and 18%, respectively.[8]

It was determined that the effect of treatment had accelerated during month 18 to 24 compared with the other 6-month timepoints (ie, 0 to 6 months, 6 to 12 months, and 12 to 18 months).[8] Importantly, GA lesion growth reductions at 24 months were similar among patients with foveal (34% monthly and 28% EOM) and extrafoveal lesions (28% monthly and 28% EOM) in the combined studies during months 18 to 24.[8]

Researchers in the 36-month GALE extension study have reported their 12-month readout (ie, 36 months from baseline).[9] After 36 months of treatment with pegcetacoplan, patients in the monthly arm experienced a 35% reduction in GA lesion growth and patients in the EOM experienced a 24% reduction compared with projected sham.[9]

Primary eye care providers may need to lay the foundation for patients that consistent follow-up with a retina specialist will be key to success: unlike wet age-related macular degeneration, patients will not realize a benefit to therapy after a few injections, but rather will need to consistently receive therapy to simply reduce the rate of disease progression and vision loss.

LESION LOCATION

In the DERBY/OAKS treatment arms, extrafoveal lesions demonstrated lower rates of GA growth compared with foveal

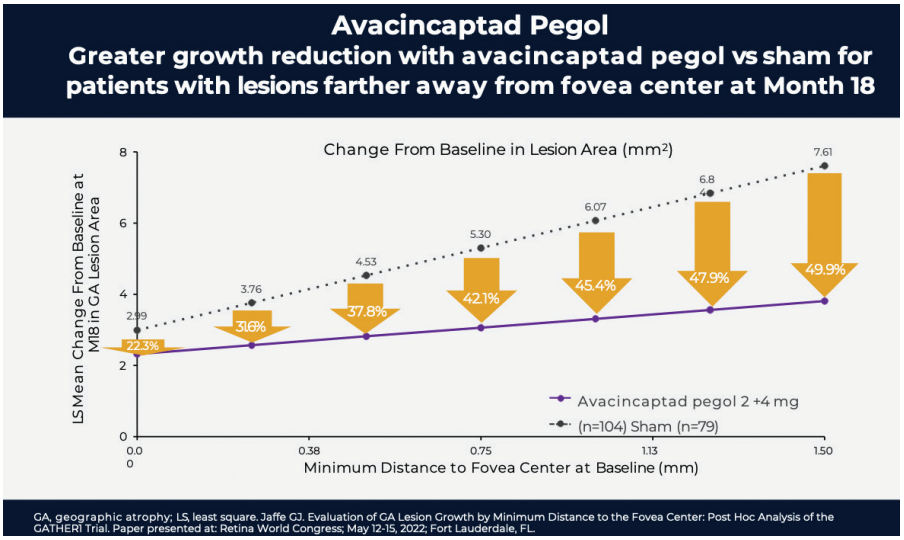


Figure 3. In GATHER1 and GATHER2 at 18 months, lesions farthest away from the foveal center demonstrated greater reductions in growth rate compared with those closer to the foveal center.

lesions, and lesions farther from the foveal center in GATHER1/2 demonstrated greater growth reduction than those near the foveal center.

In DERBY/OAKS, patients with nonsubfoveal (ie, extrafoveal) lesions at month 24 experienced reductions in GA growth rate of 26% in the monthly arm and 23% in the EOM arm (Figure 2).[10] For patients with subfoveal (ie, foveal) lesions, monthly and EOM reductions in GA growth rate were 19% and 16%, respectively.[10]

Patients in GATHER1/2 did not have foveal lesions at enrollment. However, extrafoveal lesions that were farthest away from the foveal center showed greater growth reduction rates at 18 months compared with extrafoveal lesions closest to the foveal center, with those farther from the center demonstrating reductions of nearly 50% and those closest to the center showing rates of approximately 22% (Figure 3).[11]

To the primary eye care provider, these data suggest that growth rates for extrafoveal lesions may be significantly affected by prompt referral and intervention. If we encounter GA patients with extrafoveal lesions and no visual disruption, we should still refer them promptly to a retina specialist.

SAFETY

Patients with GA may experience new-onset exudation after GA therapy. At month 12 in GATHER1/2, patients in the treatment arms experienced macular neovascularization rates of 6.7% to 9.0%, which were higher than the rates in the sham arms of 2.7% to 4.1%.[12] Pooled analysis of the DERBY and OAKS studies at 12 months showed new-onset exudation rates in the monthly, EOM, and sham groups of 6.0%, 4.1%, and 2.4%, respectively.[6] At month 24, these rates were 12%, 7%, and 3%, respectively.[13]

Intraocular inflammation (IOI) rates are of interest to eye care providers, as the complications following IOI may be significant. In GATHER1, a single instance of IOI was observed[14]; it resulted in no change to visual acuity and resolved without therapy. In DERBY/OAKS, the rate of IOI was 0.19% per injection when excluding cases linked to drug impurity from 2018.[7] The Research and Safety in Therapeutics committee at the American Society of Retina Specialists reported 21 cases of IOI in real-world patients who had been dosed with pegcetacoplan, which included one case of retinal vasculitis and seven cases of retinal occlusive vasculitis.[15] It should be noted that no cases of retinal vasculitis or retinal occlusive vasculitis were observed in DERBY or OAKS,[16] and that a review of study data did not uncover any previously unnoticed cases.[16] An estimated 68,000 vials of pegcetacoplan had been distributed at the time of the report.[16]

In a clinical sense, modest increases in exudation rates should not discourage primary eye care providers from referring patients with GA to retina specialists, as we have therapies that have been shown to be safe and effective at addressing exudative disease. Similarly, retina specialists are equipped to manage therapy-related IOI events, and primary eye care providers should not decline to refer patients for evaluation and possible treatment because of this real-world safety concern.

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The Pipeline

MARK T. DUNBAR, OD, FAAO

Many candidates in the therapeutic pipeline focus on complement inhibition, which may be unsurprising given that the only two therapies approved for GA are C3 and C5 inhibitors. Still, other complement inhibitors have failed to demonstrate safety and efficacy at various phases of research. In the 2010s, C5-inhibitors eculizumab[1] and tesidolumab,[2] and the CFD-inhibitor lampalizumab,[3] all failed to demonstrate sufficient safety and efficacy for their development to be furthered.

Still, as we have seen from the 12-month primary endpoint of the DERBY and OAKS studies, drugs that fail to reach their primary endpoint but still demonstrate a therapeutic effect could eventually end up in clinics. Take, for instance, ANX007, a C1q-inhibitor under investigation in the phase 2 ARCHER study, a 12-month trial with a primary endpoint of mean rate of change (slope) in GA lesion area compared to sham at 12 months.[4] Patients in the study were randomly assigned to monthly treatment, every-other-month treatment, or sham arms.

The study did not reach its primary endpoint, but a secondary analysis showed that the treatment effect was more pronounced in the final 6 months of the 12-month study compared with the first 6 months. This suggests that the drug may have a more pronounced effect over time, similar to the dynamic observed in the DERBY and OAKS studies at 24 months. Significantly more patients in the sham arm lost at least 15 letters at the study end compared with patients undergoing either monthly or every other month (EOM) treatment. Of note, 3.7% of treatment (ie, monthly or EOM) patients with extrafoveal lesions lost at least 15 letters at month 12 compared with 17.8% of patients with extrafoveal lesions who received sham ($P < .01$).[5]

ANX007 was generally well tolerated. Conversion to choroidal neovascularization occurred in 3.4% of sham patients and 4.5% of treatment patients, and the three intraocular inflammation cases observed were not associated with retinal vasculitis.[5]

ANX007 is far from the only complement inhibitor under investigation for the treatment of GA—indeed, there are dozens of studies assessing the safety and efficacy of complement inhibition for GA. It remains to be seen which of these drug candidates will ultimately end up in clinics, and whether they will demonstrate superiority or noninferiority to approved drugs.

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Optimizing Referrals: Case Study

CAROLYN E. MAJCHER, OD, FAAO, FORS

As outlined in my previous article, evidence shows that extrafoveal lesions respond more robustly to treatment compared with foveal lesions. If primary eye care providers detect disease early and refer promptly, we may be able to delay foveal encroachment and prolong the timespan of functional vision. Still, in my estimation, primary eye care providers should err on the side of referral upon detecting geographic atrophy (GA) in any patient, even if foveal involvement is observed and useful vision remains.

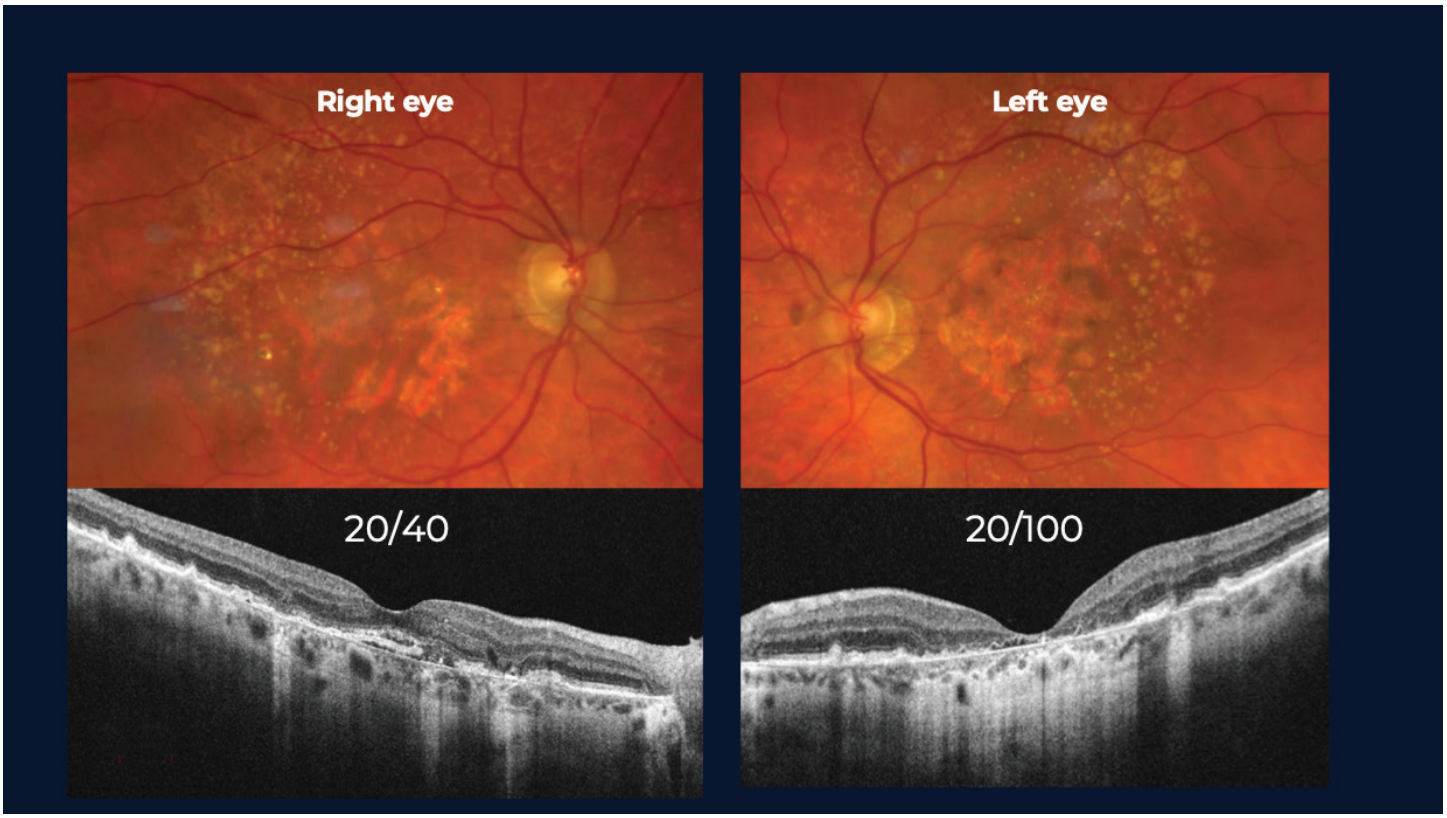
Patients may have to undergo therapy for at least 6 months to benefit, and patients who estimate that they do not have enough time to realize a benefit (ie, those at end-of-life stages) may not be good candidates for referral. Although some patients with GA may have comorbid conditions that suggest a poor prognosis (eg, patients with end-stage glaucoma), referral to a retina specialist for evaluation is often still prudent.

Primary eye care providers should educate patients about treatment expectations and burden at the time of referral. Setting realistic expectations early may make patients more receptive to treatment after meeting with a retina specialist, and it ensures that the first time they hear about chronic monthly or every-other-month injections will not be in an ophthalmologist's office. A primary eye care provider should assess whether a patient has the appetite for frequent treatment before referring.

As the first line of contact for many patients with GA, primary eye care providers are tasked with educating patients about their disease. Personalized explanations of age-related macular degeneration (AMD) and GA leveraging clear, jargon-free language is key. For patients with GA, it is important to emphasize that progression is inevitable for most and that vision loss is irreversible. Explanations of different stages of AMD may be useful (particularly for early and intermediate-stage AMD patients), and a discussion of risk factors could prove useful. Primary eye care providers should educate patients on healthy lifestyle choices, such as smoking cessation and shifting dietary patterns, before explaining how the process of a referral will work. Patients referred for consideration of GA treatment should be educated on the importance of continued self-screening for exudation at home since the risk of exudation increases with current GA therapies.

REAL-WORLD CASE

An 81-year-old woman presented to the clinic complaining of progressing decreased vision, with her left eye seeing worse than her right eye. Color fundus photography (CFP) and optical coherence tomography (OCT) imaging were performed (Figure) and BCVA measurements were captured.



Images courtesy of Carolyn E. Maicher, OD, FAAO, FORS

Figure. CFP and OCT imaging confirmed the presence of extrafoveal lesions OD and foveal lesion OS, which aligned with BCVA measurements of 20/40 OD and 20/100 OS.

Multifocal extrafoveal GA lesions were observed OD on CFP, and choroidal hypertransmission could be observed on OCT. BCVA OD was 20/40. In the contralateral eye, BCVA was 20/100, and subfoveal lesions were observed on both imaging modalities.

Prompt referral for a patient such as this one could lead to intervention in her right eye that, if successful, could significantly slow the progression of her GA lesion—and hopefully prevent foveal encroachment. Although foveal involvement is detected OS and BCVA has dropped to 20/100, the patient may still realize benefit if the left eye is treated in an attempt to slow central scotoma enlargement, as this level of vision may still allow the patient to perform some tasks.

Passing along any information about history of progression to a retina specialist may be wise, as the referring provider can use such data to contextualize the patient's disease. In this case, I had 2.5 years of imaging to send to a retina specialist, which I sent alongside other relevant data when making the referral. ■

GA in the Primary Eye Care Clinic: Improving Detection, Understanding Therapy, and Perfecting the Referral

COPE Release Date: March 1, 2024
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DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week
(with the disease targeted
in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	**Agree**	**Neutral**	**Disagree**
Summarize epidemiologic data about AMD and GA, and **identify** risk factors for AMD and GA.	_____	_____	_____
Identify the deleterious effects of AMD and GA on overall patient health, quality of life, and the health care system.	_____	_____	_____
Explain the connection between the development of GA and the complement system.	_____	_____	_____
Compare how various imaging modalities used in GA diagnosis depict disease.	_____	_____	_____
Understand the current state of the GA therapeutic pipeline.	_____	_____	_____
Anticipate how possible changes to GA treatment strategies will affect referral patterns and **recognize** ways to improve collaborative care models to ensure high-quality patient care is delivered.	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to detect geographic atrophy (GA) and refer these patients to a retina specialist (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. An 82-year-old man presents with a chief complaint of visual disturbance in his right eye. He is a smoker with a past medical history significant for hypertension, heart disease, and hyperlipidemia. He is African American. You note pigmentary abnormalities in both eyes (right eye>left) as well as numerous large drusen. All of the following represent this patient's risk factors for age-related macular degeneration (AMD) EXCEPT:

a. Older age
b. Smoking status
c. African American race
d. Hyperlipidemia

3. All of the following represent the deleterious effects of AMD and GA on patient's quality of life EXCEPT:

a. Increased time spent reading
b. Less engagement with friends
c. Need for visual aids
d. Less exercise

4. Which one of the following statements is hypothesized to be involved in the pathophysiology for GA?

a. Complement deposition at the level of the inner nuclear layer
b. Increased regulation of the complement system
c. Blood-retina barrier activation
d. Continuous low-grade complement-mediated inflammation

5. You are evaluating a 76-year-old woman with AMD. Her color fundus photo shows a distinctly demarcated area of hypopigmentation with increased visibility of choroidal vessels in her right eye, consistent with GA. Her left eye does not show any signs of GA. Which imaging modality may help you identify incomplete retinal pigment epithelial and outer retinal atrophy (iRORA), pigment epithelial detachment, and complete retinal pigment epithelial and outer retinal atrophy (cRORA) to determine this patient's likelihood of developing GA in her left eye?

a. Color fundus photography
b. Optical coherence tomography (OCT)
c. B-scan ultrasonography
d. Fluorescein angiography

6. An 85-year-old woman presents for evaluation. She has advanced GA in her left eye with hand motion vision. Her right eye has foveal-sparing GA, with a VA of 20/30. OCT imaging shows no signs of exudation in her right eye. Which of the following is the next best step in management of this patient?

a. Observation
b. Initiation of anti-VEGF therapy in her right eye
c. Initiation of complement-inhibition therapy for GA in her right eye
d. Initiation of intravitreal steroid therapy in her right eye

7. A 76-year-old woman presents for evaluation. She has bilateral extrafoveal GA that has progressed significantly over time. She is otherwise healthy and motivated to keep her eyesight. Which of the following is NOT a recommended next step for this patient?

a. Referral to a retina specialist
b. Observation at this time
c. Provide Amsler grid and AREDS
d. Advise therapy with omega-3

8. What is responsible for approximately 90% of central vision loss globally?

a. Exudative AMD
b. Cataract
c. Diabetic retinopathy
d. Retinal vascular occlusion

9. An 87-year-old Caucasian man who smokes presents for examination. He notes blurry vision in both eyes. You note diffuse punctate epitheliopathy, 1+ nuclear sclerotic cataracts, and numerous moderately sized drusen. OCT imaging reveals no signs of exudation. Which is the most important next step in management of this patient?

a. Discussion of smoking cessation
b. Cataract evaluation
c. Lifitegrast prescription
d. Brimonidine prescription

10. A 76-year-old Caucasian woman with bilateral GA presents for evaluation. She is noting increasing difficulty with reading and starting to feel disengaged from social activities. On imaging, you note her GA is extrafoveal and multifocal. Which of the following statements about her likely progression is TRUE?

a. Her GA is not likely to progress because it is extrafoveal
b. Her GA is likely to progress because it is extrafoveal and multifocal
c. Her GA is not likely to progress because it is multifocal
d. There is insufficient data given to determine if her GA is likely to progress

11. According to studies, what percentage of patients with GA who have a driver's license report not feeling confident driving during the day?

a. 25%
b. 52%
c. 75%
d. 100%

12. Genetic defects in the complement cascade accounts for what percentage of AMD heritability?

a. 10% to 20%
b. 30% to 50%
c. 40% to 60%
d. 70% to 90%

13. You are examining a 72-year-old patient with a history of AMD. Which of the following imaging modalities would most help you identify reticular pseudodrusen to determine this patient's risk profile for developing GA?

a. Color fundus photography
b. OCT
c. Fluorescein angiography
d. B-scan ultrasonography

14. You are examining an 84-year-old patient with a history of AMD with GA. He is noting increasing difficulty with his activities of daily living and is no longer able to drive. Which of the following imaging modalities can help quantify his GA into a pattern that might confer higher risk of progression, such as diffuse-trickling?

a. Color fundus photography
b. OCT
c. Fundus autofluorescence
d. B-scan ultrasonography

15. You are evaluating a 75-year-old patient with GA. She notes progressive decline in her vision during the past year, including increasing difficulty driving. You start her on pegcetacoplan monthly. What is the target molecule of this drug?

a. C3
b. C4
c. C5
d. C6

16. You are evaluating an 80-year-old patient with GA who is currently undergoing intravitreal therapy with pegcetacoplan for his GA. Which of the following statements is TRUE regarding ongoing monitoring of this patient?

a. Encourage self-monitoring and perform in clinic monitoring to check for exudative conversion
b. This patient must be screened for neovascular glaucoma every other month
c. This patient must be screened monthly for choroidal melanoma
d. This patient must be started on an IOP-lowering prophylaxis

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____No

Probability of changing practice behavior based on this activity: _____High _____ Low _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy _____
Change in nonpharmaceutical therapy _____
Change in diagnostic testing _____
Choice of treatment/management approach _____
Change in current practice for referral _____
Change in differential diagnosis _____
My practice has been reinforced _____
I do not plan to implement any new changes in practice _____

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
_____ Other. Please specify: _____

The design of the program was effective for the content conveyed	___ Yes	___ No
The content supported the identified learning objectives	___ Yes	___ No
The content was free of commercial bias	___ Yes	___ No
The content was relative to your practice	___ Yes	___ No
The faculty was effective	___ Yes	___ No
You were satisfied overall with the activity	___ Yes	___ No
You would recommend this program to your colleagues	___ Yes	___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____

This information will help evaluate this activity; may we contact you by email in 3 months to inquire if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____

_____