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AGE OF DISCOVERY: A Guide to Potential Geographic Atrophy Therapies

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AGE OF DISCOVERY:
A Guide to Potential Geographic Atrophy Therapies

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Content Source

This continuing education (CE/CME) activity captures content from a live symposium recorded October 2022.

Activity Description

This supplement summaries presentations from a live symposium that focused on geographic atrophy (GA). Although there are no approved therapies for the treatment of GA, there are numerous candidates at various stages of development. The faculty review these potential therapies as well as risk factors that drive this disease, imaging modalities that are best suited for GA evaluation, and the type of lesions patterns that place patients at high risk for progression.

Target Audience

This certified CE/CME activity is designed for optometrists and general ophthalmologists.

Learning Objectives

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

- **Summarize** the prevalence of AMD and GA and **define** the burden of illness linked specifically to GA
- **Comprehend** and **explain** the pathogenesis of GA
- **Describe** GA disease detection and factors influencing progression
- **Appraise** the therapies targeting GA that have been explored as well as those in the pipeline

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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 diagnose geographic atrophy (GA; 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. Please rate your confidence in your ability to discuss the pipeline therapies targeting GA (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

3. A 74-year-old patient presents to your office for annual examination. On dilated fundus exam, she has numerus drusen that measure ~80 µm in diameter in both eyes. What stage of age-related macular degeneration (AMD) does this patient have?

a. No AMD
b. Early AMD
c. Intermediate AMD
d. Advanced AMD

4. What percentage of patients with dry AMD progress to GA?

a. ~10%
b. ~20%
c. ~30%
d. ~40%

5. All of the following represent good tools to measure the impact of GA, EXCEPT?

a. Best corrected visual acuity
b. Reading speed assessments
c. Microperimetry
d. Low-luminance visual acuity

6. A 78-year-old man presents to your office for annual examination. He has evidence of large drusen on exam with pigmentary abnormalities. All of the following are risk factors for this condition, EXCEPT?

a. Smoking
b. Male sex
c. High-fat diet
d. Hyperopia

7. An 84-year-old patient with AMD presents to your office for evaluation. He is currently experiencing mild visual dysfunction due to his AMD, but he can still perform all of his activities of daily living. On exam, you note dry eye, bilateral brunescent cataracts, moderate drusen, and diabetic retinopathy. OCT shows evidence of subretinal drusenoid deposits. Which of the following increases his risk for progression of GA?

a. Dry eye
b. Cataracts
c. Subretinal drusenoid deposits
d. Diabetic retinopathy

8. A 78-year-old patient presents to your office with a chief complaint of progressive vision loss during the past 2 years. She has a history of mild GA. Which of the following OCT findings would indicate progression of GA?

a. Increased hyperreflective changes on OCT
b. Increased hyporeflective changes on OCT
c. Increased cystic intraretinal fluid on OCT
d. Increased subretinal fluid on OCT

9. An 85-year-old woman presents to your office for her annual dilated exam. She has numerous drusen in her left eye measuring larger than 125 µm and pigmentary changes in both eyes. What stage of AMD does she have?

a. No AMD
b. Early AMD
c. Intermediate AMD
d. Advanced AMD

10. Patients with more than a 40 pack-year history of smoking are nearly ___ more times likely to develop GA?

a. 2.5
b. 3.5
c. 4.5
d. 5.5

11. All of the following are OCT biomarkers for increased risk of advanced AMD/GA EXCEPT:

a. Intraretinal hyperreflective foci
b. Hyperreflective drusen cores
c. Subretinal drusenoid deposits
d. High central drusen volume

12. A 69-year-old woman with AMD presents to your office for evaluation. She notes increasingly blurry vision during the past 2 years. On exam, you note a central area of GA as well as 1+ nuclear sclerosis. On OCT you note an area of hypertransmission ~300 µm wide. Which of the following is TRUE?

a. Her vision loss is likely due to progressing GA, and she is at risk for further progression with time
b. Her vision loss is likely due to exudative macular degeneration, anti-VEGF injections should be initiated
c. Her vision loss is likely due to cataract progression
d. Her vision loss is unrelated to her macular degeneration

Eye care providers managing patients with advanced age-related macular degeneration (AMD) have dealt with a frustrating reality: although various treatments have been shown to be safe and effective for patients with neovascular AMD (wet AMD), no treatments have been approved by regulatory bodies for the treatment of geographic atrophy (GA). This means that we are able to simultaneously provide sight-saving care for a substantial number of our wet AMD patient population, while remaining unable to treat a meaningful number of patients with GA.

Decades of research may soon yield options that are safe and effective to prevent the progression of GA, and there is reason for optimism: as of December 2022, the FDA has accepted filing for review for two therapies intended for the treatment of GA. Given this context, a detailed discussion about AMD, in general, and GA, in particular, is essential to ensure all clinicians are able to identify GA on multiple imaging modalities.

Programs that engage audiences and allow dialogue are among the most productive types of discourse in science. With that in mind, the program we participated in prompted audience members to submit questions. We have selected a pair of those Q&A submissions as sidebars in this piece.

Each speaker at this live event was tasked with covering a particular subject, and their presentations have been adapted here. You'll also see a section covering real-world patient cases, which shows how patients with GA have experienced disease progression.

—Yasha S. Modi, MD, and SriniVas Sadda, MD, Program Co-Chairs

AMD and GA: Background, Prevalence, and Burden

YASHA S. MODI, MD

Age-related macular degeneration (AMD) is, as the name suggests, a process related to aging. As the population in the United States and the globe ages, we can expect to see increased prevalence of AMD. Current estimates place the prevalence of AMD between 11 and 19 million in the United States and 170 million globally.[1,2] By 2050, prevalence rates are estimated to increase to 22 million and 288 million, respectively, for the US and global populations.[3,4]

AMD is categorized into four stages based on fundoscopic clinical features (Figure 1).[5] The first stage (Category 1) is characterized by small drusen or drupelets (≤ 63 µm). As patients progress to early AMD, they may manifest many small or few medium-sized drusen (Category 2). Category 3, or intermediate AMD, is defined as many medium-sized drusen or one large drusen (> 125 µm). As patients progress through the intermediate stages of AMD, they may develop pigmentary changes, which portends a poor prognosis for progression to advanced disease. Finally, advanced, or Category 4 AMD, is defined as foveal-involving geographic atrophy (GA) or exudative AMD.

GA is a progressive disease that is defined as an abrupt and well-delineated loss of the retinal pigment epithelium (RPE) and choriocapillaris.[6] Approximately 85% to 95% of patients with AMD manifest dry AMD, with about 30% progressing to GA.[4,7,8] Fundus autofluorescence (FAF) imaging clearly depicts GA as a hypoautofluorescent area corresponding to loss of the RPE (and associated lipofuscin that the camera is designed to detect; Figure 2). The utility of FAF and other imaging modalities is discussed later in this piece.

Similar to how rates of AMD are forecast to increase with an aging population, so too are GA prevalence rates. GA in the United States was estimated to be 1.75 million in 2004, and grew to nearly 3 million in 2020.[9]

Several environmental or lifestyle factors contribute to the development of AMD, and some factors have been linked to GA,

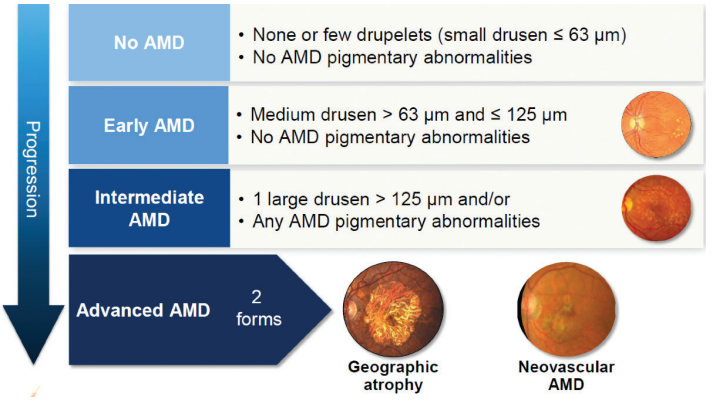

Figure 1. Requirements for staging various levels of AMD, as defined by Ferris et al. Patients are subtyped to GA or neovascular AMD when they reach the advanced AMD stage.

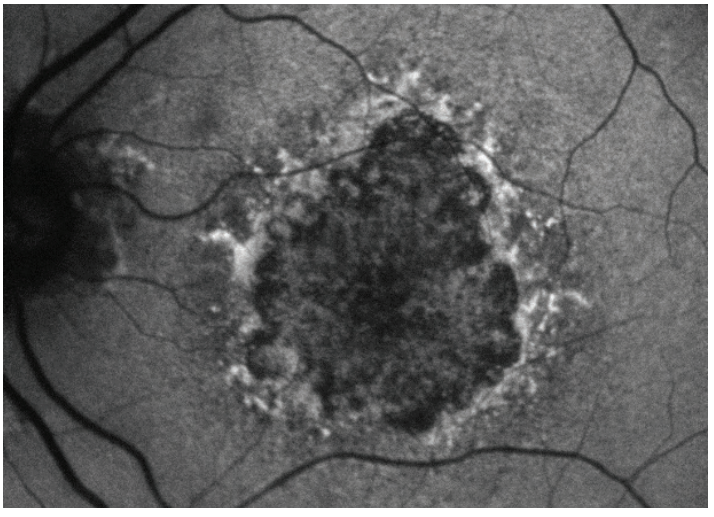

Figure 2. The hypofluorescent areas on FAF correspond to the GA, or loss of the RPE and choriocapillaris. The perilesional hyperautofluorescence may represent "sick RPE," or lost photoreceptors, that precede RPE loss (thus unmasking the hyperautofluorescence of the otherwise intact RPE).

A QUESTION FROM THE AUDIENCE

Q: What is the difference between dry age-related macular degeneration (AMD) and geographic atrophy (GA)?

A: Yasha S. Modi, MD: This is an instance in which colloquial terminology overlaps with highly technical terminology. GA is specifically an area of coalesced retinal pigment epithelium (RPE) and choriocapillaris loss with very distinct margins between the area of loss and the area of preservation, whereas we might consider dry AMD (a colloquial term) to represent any stage of AMD not characterized by exudation.

Caroline R. Baumal, MD, FASRS: I would note that the presence of GA and wet AMD—that is, the two main subtypes of advanced AMD—are not mutually exclusive. I have observed GA in some of the wet AMD patients I see for routine care.

SriniVas Sadda, MD: When working with trainees, some institutions have framed AMD as a disease that is present when medium drusen or related extracellular RPE deposits are detected, and that atrophy is the end stage of AMD. Neovascularization, in this framing, is an interval event that occurs in some patients.

in particular. Diet has been linked to AMD development, with Western diets correlated with increased risk of AMD compared with non-Western diets.[10] Obesity and hypertension have been linked with an increasing risk of AMD.[11] Exposure to ultraviolet light is also a potential risk factor for developing AMD.[12]

One of the strongest and preventable risk factors is smoking. A smoking history can be used to predict vison loss secondary to GA.[13] Patients with more than a 40 pack-year history of cigarette smoking are nearly 3.5 more times likely to develop GA.[14]

Other risk factors associated with AMD and GA cannot be controlled by patients. Increased age, white race, and the presence of particular genetic risk alleles increase the likelihood of developing AMD.[14-17] A 2020 estimate of the British population concluded that 1.3% of patients between the ages of 65 and 69 had GA.[18] This increased to nearly 12% in patients aged 85 to 90.[18] As for understanding the simplified genetic risk markers, two alleles (CFH and ARMS2) have been identified as increasing risk for AMD development.[15] Sepp et al identified the CFH variant Y402H as increasing the risk for GA development.[13] While understanding genetics is helpful for understanding pathogenesis, there is no current clinical indication to conduct genetic testing in patients.

Women are at a higher risk for developing advanced AMD compared with men. Although the reasons for this remain unknown, some researchers have proposed theories involving differences in hormonal or cerebrovascular dynamics.[19,20] Patients who are hyperopic[21] or have lighter colored irises[22] are also at increased risk of developing AMD.

When considering progression to AMD, there are some high-risk ocular features. The presence of subretinal drusenoid deposits (SDDs) has been linked with progression of GA,[23] with Finger et al finding that SDDs were an independent risk factor for developing GA in eyes without advanced AMD among patients with unilateral wet AMD.[24] In the following pages, Dr. Sadda will explore risk factors linked to disease progression among eyes with GA lesions that are depicted on FAF and OCT.

Advanced AMD and GA may severely reduce quality of life (QOL) and may exacerbate or contribute to depression. Activities such as reading, shopping, meal preparation, and self-care are significantly hindered by AMD.[25] Depression rates are higher among patients with AMD compared with patients who do not have AMD.[26] Among patients with any AMD, those with wet AMD have reported more optimistic expectations about their future and those with GA (a condition without an approved treatment) are saddened by "profound loss."[27]

Even extrafoveal GA can disrupt QOL and hamper independence. One major manifestation of this is through loss of comfort with driving. The majority of patients with GA do not feel comfortable driving during the day (52%) or night (88%), regardless of the location of GA lesions.[28] Chakravarthy et al have determined that 67% of UK patients with bilateral GA were ineligible to drive at mean 1.6 years following their diagnosis.[29]

MEASURING VISUAL DISRUPTION IN GA PATIENTS

Given the foveal-sparing nature of some GA, conventional measurements of BCVA may inadequately characterize a patient's "true" quality of vision.[30,31] Alternative assessments of visual function, such as low-luminance visual acuity (LLVA), reading speed, questionnaires, and microperimetry have been used by some researchers and clinicians to better assess these deficits.

Patients with GA often have difficulty seeing in dimly lit environments. LLVA evaluations, which require patients to read letters from an ETDRS chart viewed through a neutral density filter, may demonstrate poorer testing relative to BCVA alone. Additionally, greater discrepancies between LLVA and BCVA testing may predict progression of GA.[32,33] Reading speed, too, has been an effective tool at predicting vision loss in GA patients with good baseline BCVA. This method assesses whether the "central visual field is preserved enough to read entire words or sentences" compared with individual letters as seen on a typical BCVA evaluation.[30] The National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) has been found to be a "reliable and valid cross-sectional measure of the impact of GA on patient visual function and vision-related quality of life," but real-world clinical usage remains unknown.[34]

Microperimetry testing allows clinicians to identify areas of scotoma and measure functional GA progression.[32] During microperimetry testing, specific areas of retinal tissue are stimulated with light and patients acknowledge perception by

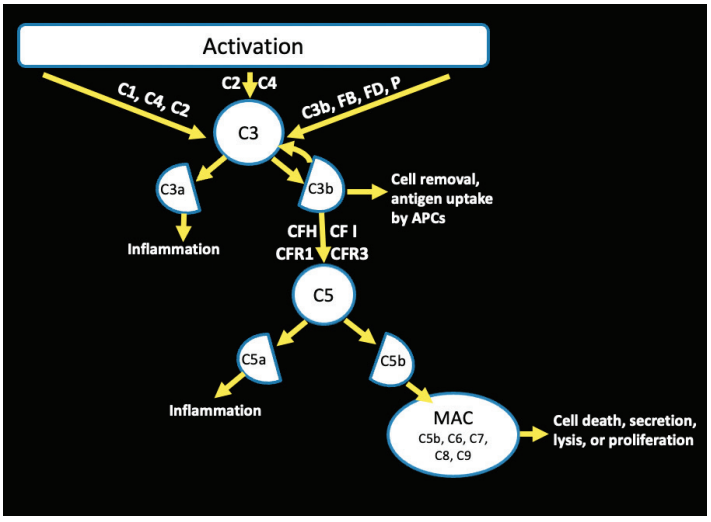

Figure 3. In this simplified rendering of the complement system, C3, C5, and MAC serve as the points of emphasis. All three activation pathways converge at C3. Further downstream, C5 is activated following cleavage of C3. Following the cleavage of C5 into C5a and C5b, C5b combines with C6 to C9 to form the MAC complex.

pressing a button. Microperimetry has been shown to correlate with progression of GA lesion area.[35]

PATHOPHYSIOLOGY AND THE COMPLEMENT SYSTEM

The exact pathophysiology of GA remains unknown. There is a plethora of hypotheses that all favor a multifactorial approach involving environmental factors, genetic factors, and oxidative stress. This may result in complement deposition between the RPE and Bruch membrane, loss of complement regulation, localized inflammation, and a breakdown of the blood-retina barrier.[36,37]

Drusen are the hallmark clinical feature of AMD. A close examination of the composition of drusen reveal some compelling findings that have informed potential therapeutic strategies for GA. Drusen are lipid- and protein-rich extracellular debris found beneath the RPE.[36] Wang et al determined that 40% of drusen are lipid, and that RPE secretions are a major source of drusen.[38] Complement factors C1q, C3, C5, and C5b to C9 have been found in drusen, implicating the complement system in the formation of drusen.[36]

The complement system is part of the innate immune system, a system that protects the body from foreign pathogens and does not adapt as we age. There are three pathways in the complement system (ie, the classical, lectin, and alternative pathways), each of which is activated via distinct mechanisms. Specifics areas of focus for the purposes of this discussion include complement component 3 (C3), where the three complement pathways first converge; complement component 5 (C5), which is further downstream from C3 and is activated following the cleavage of C3; and the membrane attack complex (MAC), the creation of which ultimately results in cell death, is assembled following cleavage of C5 (Figure 3).[39]

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Imaging in the Diagnosis and Prognostication of GA

SRINIVAS SADDA, MD

A variety of imaging modalities may be used to assess geographic atrophy (GA). These include color fundus photography (CFP), confocal fundus autofluorescence (FAF), and OCT. The benefits and drawbacks of these various modalities, some of which I will describe herein, have been explored in the literature.[1]

CFP has been the gold standard modality for diagnosis of GA. In their evaluation of various imaging modalities for use in GA, the Classification of Atrophy Meeting (CAM) Group noted that the classical definition of GA as imaged on CFP requires sharply demarked borders, a hypopigmented or depigmented appearance, and visibility of choroidal vessels in an atrophic area (Figure 1).[1]

Although this definition is useful in many cases, insufficient border contrast, particularly in the setting of media opacity or poor

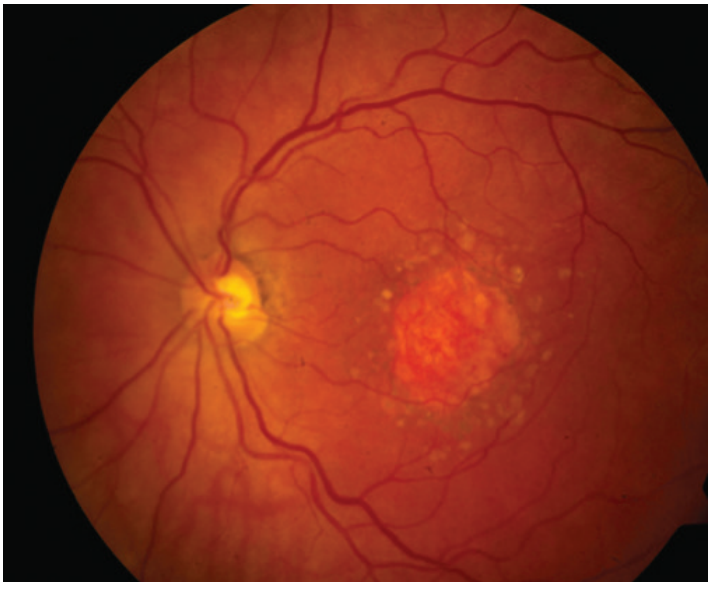

Figure 1. GA as depicted on this CFP shows sharp demarcation of a lesion area, hypopigmentation, and increased visibility of choroidal vessels.

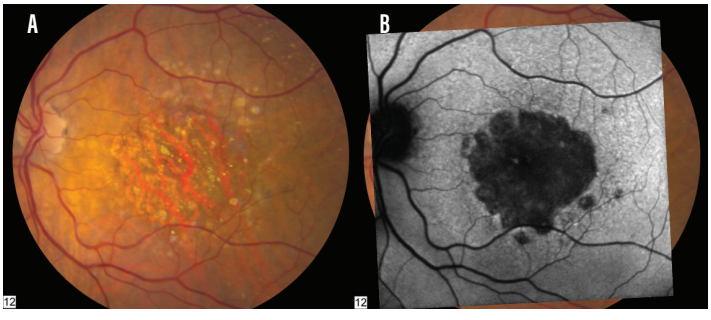

Figure 2. (A) In some cases, the borders of GA are difficult to define on CFP alone. (B) An overlay of FAF imaging clearly depicts the GA lesion as a well-demarcated region of decreased autofluorescence in the same eye.

REAL-WORLD PATIENT CASES

CASE 1: EXPANDING MULTIFOCAL LESIONS

SriniVas Sadda, MD: An 84-year-old woman with bilateral pseudophakia and advanced glaucoma in her right eye presented to the clinic in 2017 reporting increased difficulty driving through tunnels. Her BCVA is 20/25 in her left eye. Fundus autofluorescence (FAF) revealed multifocal lesions in the extrafoveal region, with hyperautofluorescence at the border of various lesions (Figure 1A).

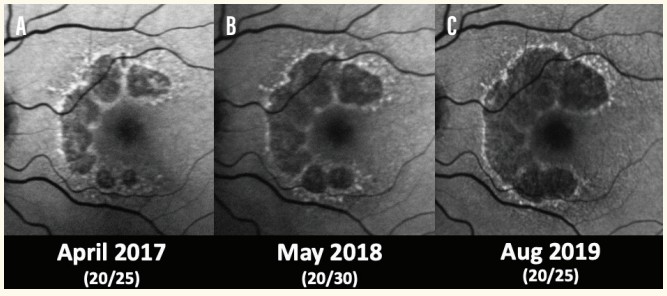

Figure 1. The growth of lesions as seen on FAF is clear over the course of 2 years, with eventual coalescence of lesions.

Caroline R. Baumal, MD, FASRS: What does a conversation with this patient look like?

Dr. Sadda: I would be careful and honest with this patient, telling her that I see some features that suggest that her vision may worsen quickly, and that she needs close monitoring. I'd also tell this patient that if a treatment becomes available, she is a good candidate for it. Atrophy has not progressed to the foveal center, which means we may be able to preserve vision if treatment can contain lesions to the extrafoveal region.

The patient returned 1 year later, with signs of progression (Figure 1B). Her BCVA was 20/30. Dr. Modi, what concerns you about this development?

Yasha S. Modi, MD: Two major elements of this patient's progression are important to note. First, her lesions have grown in absolute size. Second, her lesions are growing toward the fovea. A patient like this would have been a great candidate for a clinical trial. If this patient presented to me today, I'd note that she is a good candidate for a treatment if and when the FDA approves a therapy.

Dr. Baumal: When this patient returned the following year, coalescence of lesions could be seen on FAF (Figure 1C). On OCT imaging, an area of hypertransmission larger than 250 µm corresponding with the lesion location and a zone of attenuation of the retinal pigment epithelium (RPE) larger than 250 µm can be seen (Figure 2). Given this imaging evidence, this patient fits the qualifications for complete RPE and outer retinal atrophy, or cRORA.

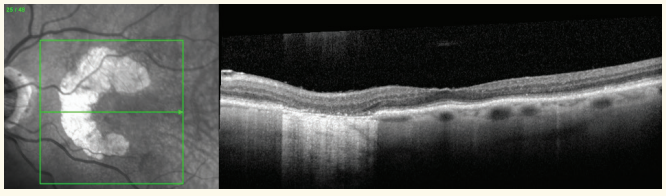

Figure 2. OCT imaging 2 years after initial presentation shows evidence of cRORA.

CASE 2: RAPID PROGRESSION NEAR THE FOVEA

Dr. Baumal: An 84-year-old woman was referred to a retina specialist for wet age-related macular degeneration (AMD) in her left eye. The patient has bilateral pseudophakia. Her left eye's BCVA is 20/25. Anti-VEGF therapy was initiated. Upon examination, her right eye's BCVA was 20/50. OCT imaging revealed evidence of geographic atrophy (GA; Figure 3) with a small focus near the fovea (Figure 4A).

Dr. Sadda: This patient's OCT imaging clearly shows areas of hypertransmission. Although portions of the RPE are still intact, this patient is likely to experience disease progression.

REAL-WORLD PATIENT CASES

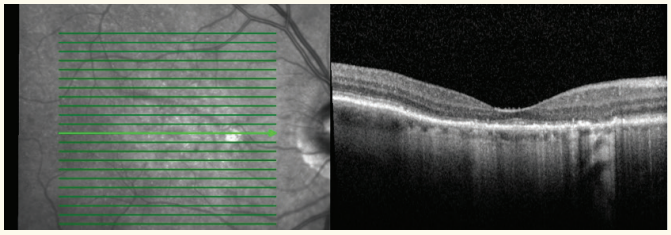

Figure 3. Evidence of hypertransmission on OCT near the fovea suggests that progression of atrophy is possible.

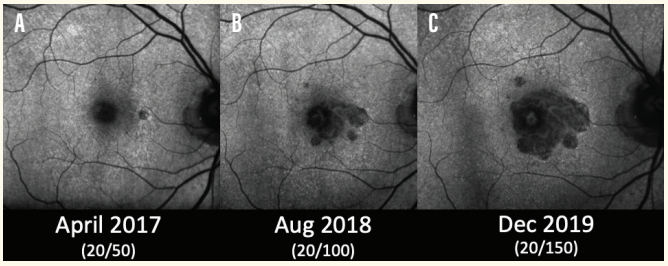

Figure 4. Lesion growth spread to the foveal center within 2.5 years of presentation.

Dr. Modi: By August 2018, the patient's BCVA was 20/100, and marked progression of GA was observed (Figure 4B). Two-and-a-half years after presentation, lesions had spread to the foveal center and BCVA was 20/150 (Figure 4C).

Dr. Baumal: If a therapy for GA is approved, patients with wet AMD in one eye and GA in the other may need to be treated with two different dosing regimens and agents. We will need to carefully plan how to proceed with treatment strategies for such patients.

NOTE: Both cases are courtesy of Roger Goldberg, MD, MBA.

stereopsis, sometimes complicates diagnosis or characterization of GA on CFP alone. Use of FAF may provide more consistent and clear depiction of the atrophic region, which is represented on the FAF image as an area of decreased autofluorescence (Figure 2). FAF allows clinicians to better quantify GA lesion area, and has been called the "gold standard for evaluating progressive GA enlargement."[2] For this reason, FAF has been used in clinical trials evaluating the safety and efficacy of potential GA therapies. Still, FAF is uncomfortable for patients and may not be as widely available in ophthalmic and optometric clinical practices as OCT.

OCT imaging remains an important part of the imaging framework for GA, in part because of its ubiquity in offices, the degree of patient comfort it allows, and its ability to provide cross-sectional assessment of all of the tissues impacted by the atrophy process, including the neurosensory retina, retinal pigment epithelium (RPE), and inner choroid. Areas of choroidal hypertransmission as seen on B scan serve as a feature to rapidly screen for regions of potential atrophy (Figure 3), and use of en face OCT images can be used to depict and quantify atrophy from a fundus perspective (Figure 4).

FAF and OCT measures of atrophy have shown a high degree of agreement, although it should be noted that these two modalities may not be measuring the same thing despite their high correlation.[3] Also, OCT may not be specific enough for all cases. Hypertransmission may indicate total cell loss, but it may also merely indicate loss of pigment in the RPE. In addition, the

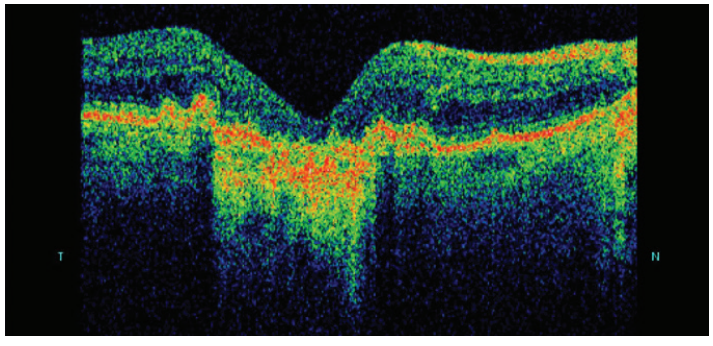

Figure 3. Areas of hypertransmission seen on OCT imaging indicate areas of atrophy.

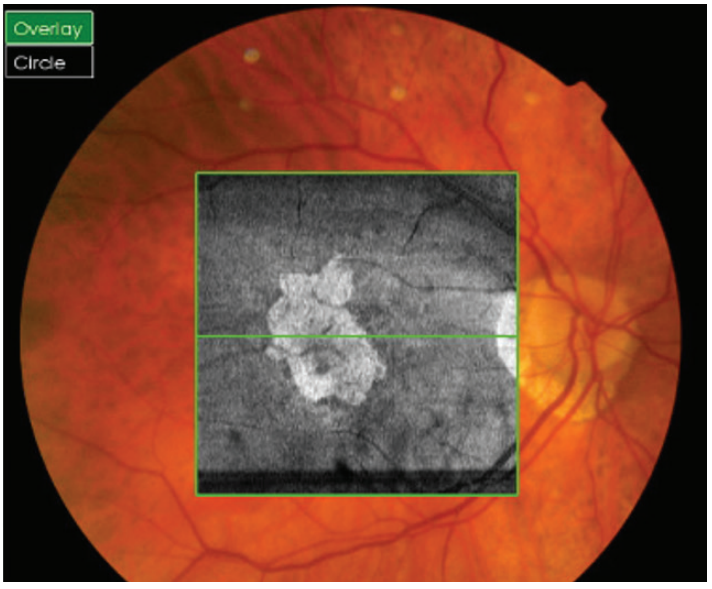

Figure 4. En face OCT image overlayed onto the CFP image. En face OCT imaging allows clinicians to identify, quantify, and monitor GA lesions with a commonly available technology.

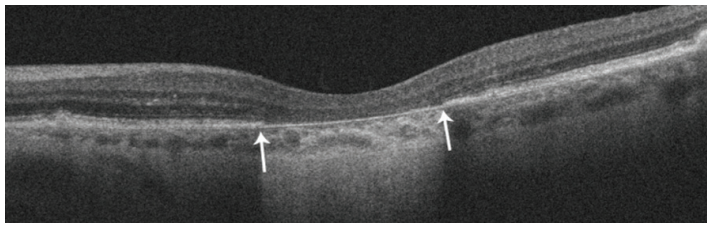

Figure 5. cRORA is present in this patient. The four qualifying criteria: an area of hypertransmission of at least 250 µm, a zone of attenuation of the RPE of at least 250 µm, evidence of overlying photoreceptor degeneration, and the absence of scrolled RPE or other signs of an RPE tear.

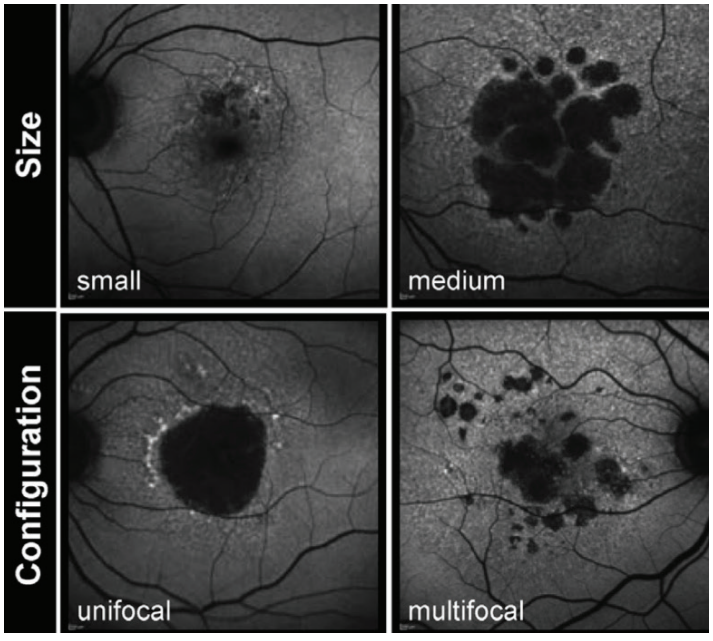

Figure 6. Patients with unifocal and/or small lesions are likely to experience slower GA enlargement than patients with larger and/or multifocal lesions. (Fleckenstein et al. *Ophthalmology*. 2018;125(3):369-390.)

extent of injury and loss to the overlying neurosensory retina may vary within regions of hypertransmission.

In an effort to classify and reliably define atrophy, the CAM consensus program was convened; I was fortunate enough to be a part of that event. My colleagues and I concluded that there was no previously accepted definition of atrophy as seen on OCT, and the features associated with atrophy or risk for progression to atrophy were not well defined. We examined cases of patients whose multimodal imaging did not, at first, suggest the presence of GA, but whose GA evolved over the course of several visits. By assessing the OCT images of these patients, we aimed to identify which characteristics appeared to define the definite presence of atrophy on OCT.

One of the terms we defined is complete RPE and outer retinal atrophy (cRORA).[4] Patients have cRORA if the following criteria are met:

- A zone of hypertransmission that is at least 250 µm in diameter
- A zone of attenuation or disruption of the RPE–basal lamina complex that is at least 250 µm in diameter
- Degeneration of the overlying photoreceptors with outer nuclear layer thinning, external limiting membrane loss, and ellipsoid zone loss
- No evidence of scrolled RPE or other signs of RPE tear

Many clinicians focus on identifying hypertransmission on OCT for good reason: it may be the most obvious and important finding and, in busy clinics, it can be quickly identified. Still, confirmation that hypertransmission is linked with the features of atrophy is needed, and using evidence of overlying RPE and photoreceptor degeneration validates any suspicions that hypertransmission is indeed the result of GA. The CAM also determined that, in order for areas of hypertransmission and RPE defect to be measured in a reproducible manner, a threshold of 250 µm was appropriate (Figure 5).[4]

PROGNOSTICATION OF GA LESION GROWTH

If and when treatments for GA are approved by regulatory bodies, eye care providers may be tasked with identifying patients who stand to benefit the most from therapy by detecting which patients are at risk for the most rapid progression of GA lesions. Use of imaging data, particularly from FAF and OCT findings, will be key in these efforts.

Classification of lesion size and pattern can be used to estimate the rate of GA progression (Figure 6). Large lesions or those with multifocal patterns progress faster than small or unifocal lesions.[5] This may be in part because GA lesions tend to expand from their borders, and the total perimeter of large and/or multifocal lesions are greater than those of small and/or unifocal lesions.

Lesions can be typed based on their location and degree of autofluorescence at their edges. A pattern of hyperautofluorescence that appears to surround the lesion along its margin is termed a "banded" pattern, and has been shown to be associated with more rapid enlargement of the GA lesion.[6] In addition, lesions with hyperautofluorescence not only at the lesion margin but also in surrounding regions are deemed to have a "diffuse"

A QUESTION FROM THE AUDIENCE

Q: How do you use OCT to image geographic atrophy in your day-to-day practice?

A: SriniVas Sadda, MD: OCT is my preferred modality for identifying and characterizing atrophy during a routine clinical examination. Part of the reason I use OCT is that the definition of cRORA, which relies on OCT images, is clear and quantifiable. It is important to capture sufficient density of B-scans during volume OCT acquisition so that en face OCT image can be generated. I advise anyone using OCT to screen for and characterize atrophy look for hypertransmission, which is easy to spot on an OCT image of good quality.

pattern, which is also associated with faster GA growth.[6-9] Some GA lesions with diffuse patterns have a grayish (rather than black) hypoautofluorescence that may be a sign of a "diffuse-trickling" pattern, which is particularly suspectable to rapid growth.[6-9]

In practical terms, I do not think that clinicians will be obliged to extensively characterize the lesions of patients with GA as having particular sizes or as having specific patterns or autofluorescence features. Rather, eye care providers who are aware of the relationship between size, shape, and autofluorescence patterns can use such information to broadly assess the risk of rapid disease progression, thereby triaging which patients are best suited for immediate intervention. This, of course, assumes that a treatment will soon be approved.

OCT imaging, too, may be used to assess the risk for more rapid progression. For example, reticular pseudodrusen (RPD), also called subretinal drusenoid deposits (SDD), are drusen that accumulate above the RPE (rather than below the RPE, as drusen do). RPD appear to confer an increased risk of progression from AMD to GA and for progression of GA.[10]

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Latest Update on the GA Pipeline

CAROLINE R. BAUMAL, MD, FASRS

Multiple therapeutic agents are being explored to treat or prevent the progression of geographic atrophy (GA). Many of these potential treatments target the complement pathway, while a handful of others attempt to address GA via other routes. I will review some selected therapies here.

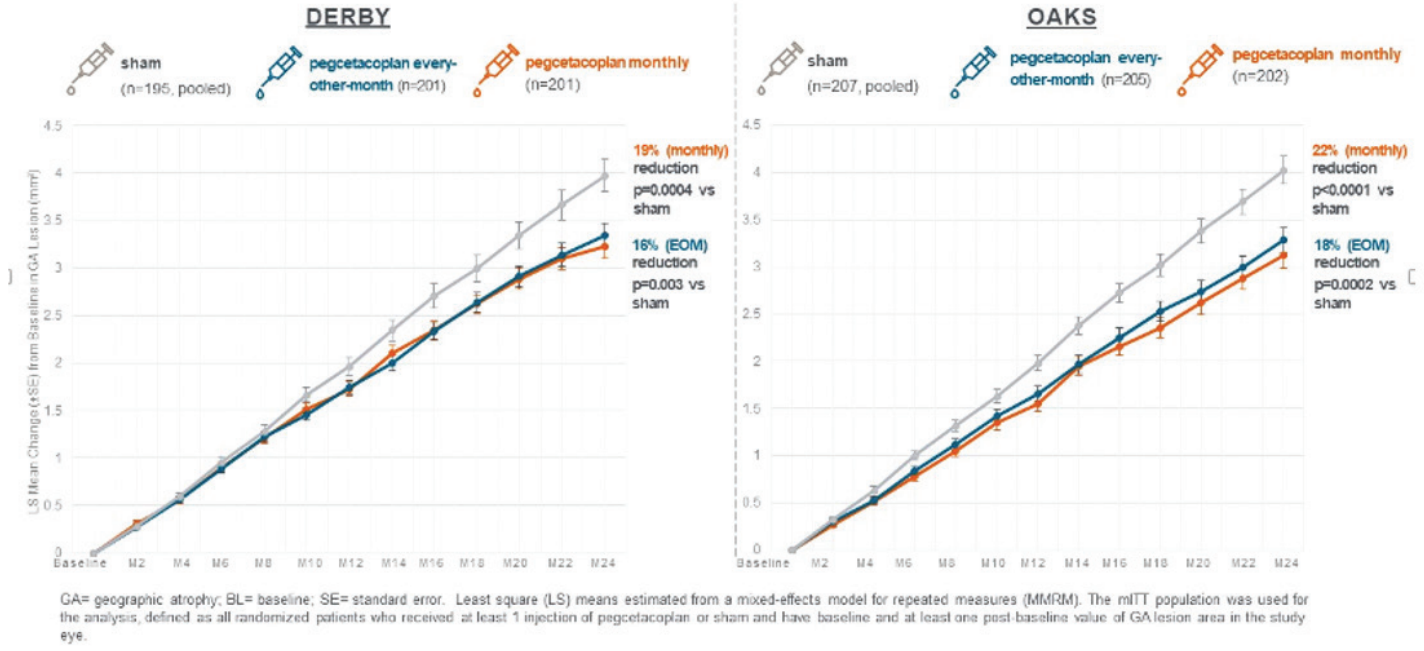
FIRST GENERATION OF COMPLEMENT INHIBITORS

Several early complement inhibitors were examined for the treatment of GA, all of which failed to show sufficient efficacy in phase 2 or phase 3 studies. The C5 inhibitor eculizumab was assessed in the phase 2 COMPLETE study, a prospective, double-masked, randomized clinical trial.[1] Eculizumab was administered via an intravenous route. At 26 weeks, eculizumab therapy did not reduce GA lesion growth rate.[1] The C5 inhibitor tesidolumab, which was delivered via intravitreal injection, failed to demonstrate a reduction in GA lesion growth.[2] The complement D inhibitor lampalizumab was assessed for the treatment of GA in the phase 3 Spectri and Chroma studies.[3] Patients who received intravitreal lampalizumab every 4 or 6 weeks failed to demonstrate a reduction in GA enlargement compared with patients who received sham therapy every 4 or 6 weeks.[3]

MORE RECENT GENERATION OF COMPLEMENT INHIBITORS

The inability of the preliminary complement inhibitors to reduce the growth rate of GA lesions did not discourage other groups from assessing the safety and efficacy of other complement inhibitors. Two complement inhibitors—pegcetacoplan and avacincaptad pegol—have submitted filings with the FDA for the treatment of GA. Several others are in earlier stages of clinical development.

Pegcetacoplan, which binds to C3 and C3b, is delivered via intravitreal injection. The DERBY and OAKS studies are a pair of phase 3, 24-month, randomized, double-masked, sham-controlled trials that evaluated the safety and efficacy



GA= geographic atrophy; BL= baseline; SE= standard error. Least square (LS) means estimated from a mixed-effects model for repeated measures (MMRM). The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.

Figure 1. At 24-months in the DERBY and OAKS studies, reductions in GA lesion growth rate were pronounced (nominal $P \leq .003$). These data were included in an amended NDA submission to the FDA.

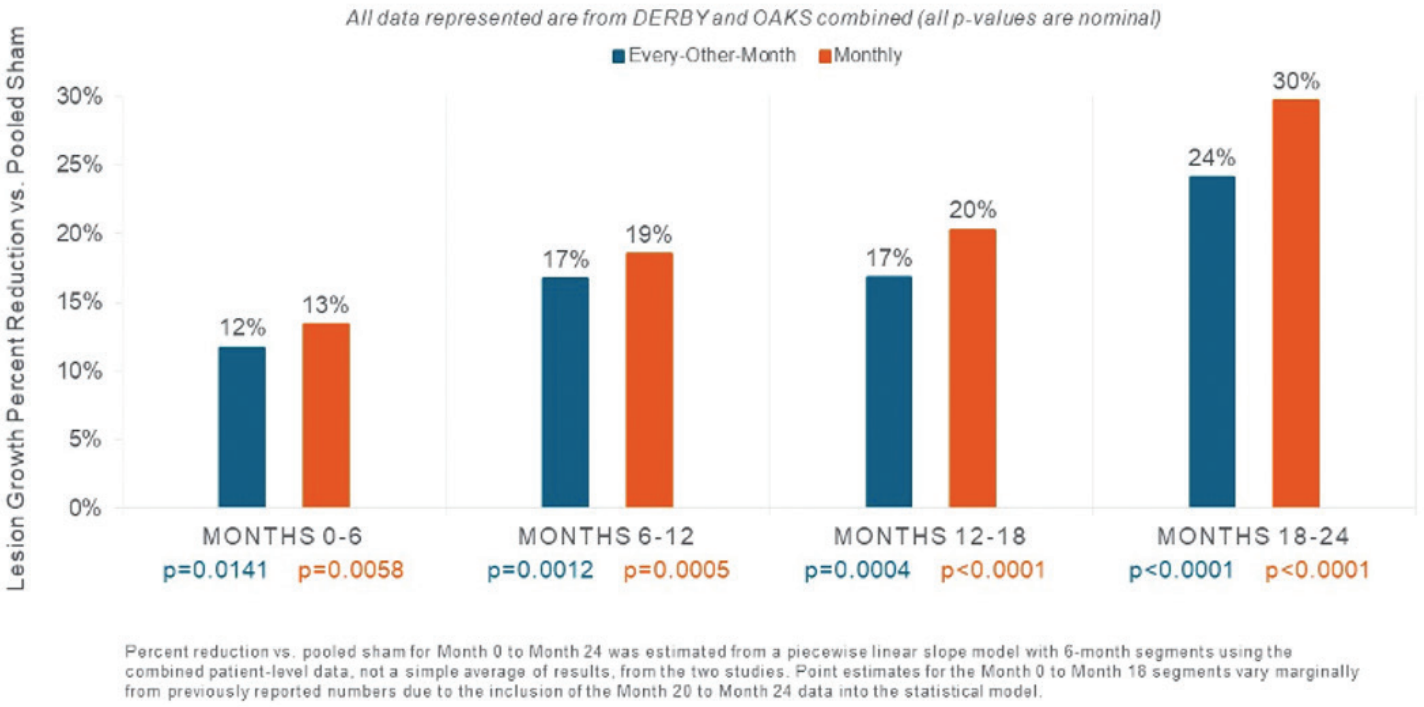


Figure 2. Pegcetacoplan's treatment effect accelerated over time during the DERBY and OAKS studies compared with pooled sham. The greatest effect was observed during months 18 to 24.

of pegcetacoplan to treat GA.[4] The DERBY and OAKS studies were informed by the phase 2 FILLY study, which found that pegcetacoplan therapy reduced the rate of GA growth by 29% and 20% with monthly and every-other-month (EOM) dosing, respectively, at month 12; both rates were statistically significant.[5] The effect was greater during the second 6 months of treatment during the first year.[5]

The phase 3 DERBY and OAKS studies randomly assigned patients to one of four arms: pegcetacoplan 15 mg/0.1 mL (monthly or EOM) or sham (monthly or EOM). In these large studies, more than 800 patients were in the pegcetacoplan treatment groups. The primary endpoint was the change in total area of GA lesions based on fundus autofluorescence (FAF) imaging at month 12. A series of endpoints (at month 24) assessing function and subjective patient responses will be reviewed. The GALE extension study will assess patients for an additional 3 years.[4] Note that inclusion criteria for the DERBY and OAKS trials allowed patients with foveal and extrafoveal lesions to enroll in the study, which makes it distinct from some other studies in GA that only enrolled patients with extrafoveal GA lesions.

In OAKS, a statistically significant reduction in GA lesion growth was observed in the monthly (22% reduction) and EOM (16% reduction) arms compared with pooled sham patients.[4] Among patients with extrafoveal lesions, the reduction rates of GA growth in the monthly and EOM arms were 25% and 21%, respectively, and both were statistically significant.[4] DERBY barely missed the statistical primary endpoint at 12 months, which reduction rates on monthly and EOM arms at 12% and 11%, respectively.[4]

A prespecified analysis of the 12-month data combining the DERBY and OAKS studies found a reduction of GA lesion growth rate of 17% and 14% in monthly and EOM arms, respectively.[4] When only looking at patients with extrafoveal lesions, the monthly and EOM GA lesion growth reduction rates were 26% and 23%, respectively.[4]

Researchers evaluated 18- and 24-month study results in DERBY and OAKS and found meaningful reductions in GA lesion growth rate observed in each study, with monthly/EOM reductions of 22%/16% in OAKS and 13%/12% in DERBY at 18 months (nominal $P < .002$).[6] This continued at month 24, where reductions in GA lesion growth rate in monthly/EOM arms were 22%/18% in OAKS and 19%/16% in DERBY (nominal $P < .003$; Figure 1).[7]

Notably, the treatment effect of pegcetacoplan accelerated over time during the DERBY and OAKS studies, being the greatest at months 18 to 24 compared with earlier 6-month quartiles (Figure 2).[7] In pooled study results, GA lesion growth reduction was similar among patients with foveal (34% monthly, 28% EOM) and extrafoveal (28% monthly, 28% EOM) lesions during months 18 to 24.[7]

Overall safety from intravitreal injection of pegcetacoplan was acceptable in DERBY and OAKS. Cases of intraocular inflammation were mild, and there were no instances of retinal vasculitis or retinal vein occlusion.[4] A total of 6.0%, 4.1%, and 2.4% of patients in the combined monthly, EOM, and sham groups,

respectively, experienced new-onset investigator-determined exudative AMD.[4] The endophthalmitis rate was 0.47%.[4]

The new drug application (NDA) filing with the FDA for pegcetacoplan was amended to include this 24-month long-term data, with decision pending February 26, 2023.[8]

Avacincaptad pegol is a C5 inhibitor that was assessed in the GATHER1 study, where patients with nonfoveal GA were randomly assigned to receive monthly intravitreal avacincaptad pegol at 2-mg or 4-mg doses or sham.[9] Patients in the 2-mg and 4-mg treatment arms, respectively, experienced reductions in GA lesion growth at month 12 of 27.4% and 27.8%; both reduction rates were statistically significant.[9]

The data from GATHER1 were used to inform the phase 3 GATHER2 study. In GATHER2, patients were randomly assigned to 2 mg monthly avacincaptad pegol or sham.[10] The mean rate of change of GA growth at month 12 was the primary endpoint. Areas of GA lesion growth were measured with a square root transformation formula and with an observed rate of growth. The difference in mean rate of growth using square root transformation was 14.3%, which was statistically significant. The difference in observed rate of GA growth was 17.7%, and the GATHER2 met its primary endpoint.[10] At month 12 in GATHER2, patients in the treatment arm were randomly assigned to monthly or EOM dosing regimens and will be assessed again at month 12.[11]

Avacincaptad pegol was well-tolerated across both studies, with no instances of endophthalmitis or ischemic optic neuropathy, and one instance of intraocular inflammation, which was considered transient and mild.[10] In GATHER1, 9.0% and 2.7% of eyes in the 2-mg treatment arm and the sham arm had choroidal neovascularization (CNV); in GATHER2, those rates were 6.7% and 4.1%, respectively.[10] The company completed its NDA filing with the FDA in December 2022.[12]

NGM621 is a C3 inhibitor assessed in the phase 2 CATALINA study, which randomly assigned 212 patients to NGM621 or sham every 4 or 8 weeks.[13] The primary endpoint was the change from baseline in the GA lesion area at 48 weeks as measured on fundus autofluorescence. At week 52, the rates of change in GA lesion area were 6.3% and 6.5% in the 4-week and 8-week treatment arms. Neither rate was statistically significant.[14]

ANX007 is a C1q inhibitor that is under investigation in the phase 2 ARCHER study, topline data from which are expected in the first half of 2023.[15] Results from a phase 1b study found that ANX007 was well-tolerated and that complete suppression of C1q target was achieved for at least 4 weeks at the highest dosing levels in patients with GA.[15] The phase 2 study has completed enrollment and results are pending.

NONCOMPLEMENT THERAPIES IN THE PIPELINE

The use of stem cell therapy has been explored for the treatment of GA. Such treatment may be used to replace lost retinal pigment epithelium (RPE) cells or to support the survival of photoreceptor and RPE.[16] An interim analysis of a phase 1/2a study exploring the use of a composite implant comprised of a stem cell-derived RPE in patients with nonneovascular age-related macular degeneration (NNAMD) found that no patients in the study lost vision and that 1 patient improved by 17 letters.[16]

Neuroprotective strategies to support photoreceptor and RPE survival, repair mitochondrial dysfunction, or treat oxidative stress have been evaluated. The neuroprotective agent elamipretide was evaluated in the phase 2 ReCLAIM-2 study, but failed to reach its primary endpoint.[17]

A photobiomodulation (PBM) platform was evaluated for the treatment of NNAMD in the phase 3 LIGHTSITE III study, in which patients were randomly assigned to receive PBM therapy or sham for 24 months.[18] The study found that PBM treatment resulted in an increase of mean 5.5 letters from baseline at 13 months compared with sham treatment, which was statistically significant.[18] No significant increase in drusen pathology was observed in the treatment arm, and numerical increases of drusen deposition were observed in the sham group.[18] ■

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AGE OF DISCOVERY: A GUIDE TO POTENTIAL GEOGRAPHIC ATROPHY THERAPIES

Release Date: January 20, 2023
Expiration Date: January 5, 2024

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached **Pretest/Posttest/Activity Evaluation/Satisfaction Measures** Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, go to https://evolvemeded.com/course/2227-2-supp. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

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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 the prevalence of AMD and GA and **define** the burden of illness linked specifically to GA	_____	_____	_____
Comprehend and **explain** the pathogenesis of GA	_____	_____	_____
Describe GA disease detection and factors influencing progression	_____	_____	_____
Appraise the therapies targeting GA that have been explored as well as those in the pipeline	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to diagnose geographic atrophy (GA; 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. Based on this activity, please rate your confidence in your ability to discuss the pipeline therapies targeting GA (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

3. A 74-year-old patient presents to your office for annual examination. On dilated fundus exam, she has numerus drusen that measure ~80 µm in diameter in both eyes. What stage of age-related macular degeneration (AMD) does this patient have?

a. No AMD
b. Early AMD
c. Intermediate AMD
d. Advanced AMD

4. What percentage of patients with dry AMD progress to GA?

a. ~10%
b. ~20%
c. ~30%
d. ~40%

5. All of the following represent good tools to measure the impact of GA, EXCEPT?

a. Best corrected visual acuity
b. Reading speed assessments
c. Microperimetry
d. Low-luminance visual acuity

6. A 78-year-old man presents to your office for annual examination. He has evidence of large drusen on exam with pigmentary abnormalities. All of the following are risk factors for this condition, EXCEPT?

a. Smoking
b. Male sex
c. High-fat diet
d. Hyperopia

7. An 84-year-old patient with AMD presents to your office for evaluation. He is currently experiencing mild visual dysfunction due to his AMD, but he can still perform all of his activities of daily living. On exam, you note dry eye, bilateral brunescent cataracts, moderate drusen, and diabetic retinopathy. OCT shows evidence of subretinal drusenoid deposits. Which of the following increases his risk for progression of GA?

a. Dry eye
b. Cataracts
c. Subretinal drusenoid deposits
d. Diabetic retinopathy

8. A 78-year-old patient presents to your office with a chief complaint of progressive vision loss during the past 2 years. She has a history of mild GA. Which of the following OCT findings would indicate progression of GA?

a. Increased hyperreflective changes on OCT
b. Increased hyporeflective changes on OCT
c. Increased cystic intraretinal fluid on OCT
d. Increased subretinal fluid on OCT

9. An 85-year-old woman presents to your office for her annual dilated exam. She has numerous drusen in her left eye measuring larger than 125 µm and pigmentary changes in both eyes. What stage of AMD does she have?

a. No AMD
b. Early AMD
c. Intermediate AMD
d. Advanced AMD

10. Patients with more than a 40 pack-year history of smoking are nearly ___ more times likely to develop GA?

a. 2.5
b. 3.5
c. 4.5
d. 5.5

11. All of the following are OCT biomarkers for increased risk of advanced AMD/GA EXCEPT:

a. Intraretinal hyperreflective foci
b. Hyperreflective drusen cores
c. Subretinal drusenoid deposits
d. High central drusen volume

12. A 69-year-old woman with AMD presents to your office for evaluation. She notes increasingly blurry vision during the past 2 years. On exam, you note a central area of GA as well as 1+ nuclear sclerosis. On OCT you note an area of hypertransmission ~300 µm wide. Which of the following is TRUE?

a. Her vision loss is likely due to progressing GA, and she is at risk for further progression with time
b. Her vision loss is likely due to exudative macular degeneration, anti-VEGF injections should be initiated
c. Her vision loss is likely due to cataract progression
d. Her vision loss is unrelated to her macular degeneration

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:

_____

_____ I certify that I have participated in this entire activity.

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.

_____

_____