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MODERN OPTOMETRY

GEOGRAPHIC ATROPHY: BEST PRACTICES FOR DIAGNOSIS & REFERRAL

A CE/CME activity provided by Evolve Medical Education LLC.

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GEOGRAPHIC ATROPHY: BEST PRACTICES FOR DIAGNOSIS & REFERRAL

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CONTENT SOURCE

This continuing medical education (CE/CME) activity captures content from Apellis Pharmaceuticals.

ACTIVITY DESCRIPTION

This roundtable discussion brings together optometric and ophthalmic experts in retinal disease to discuss the state of geographic atrophy (GA), how best to manage patients, and the pipeline therapies that have the potential to significantly alter the course of disease or many patients.

TARGET AUDIENCE

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

LEARNING OBJECTIVES

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

- **Discuss** the prevalence of AMD
- **Articulate** the burden of illness linked to GA
- **Understand** the pathogenesis of GA
- **Describe** disease detection and factors influencing progression
- **Review** the therapeutic interventions that have been explored as well as those in the pipeline

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PLEASE COMPLETE PRIOR TO ACCESSING THE MATERIAL AND SUBMIT WITH POSTTEST/ACTIVITY EVALUATION/ SATISFACTION MEASURES INSTRUCTIONS FOR CE/CME CREDIT.

1. Please rate your confidence in your ability to understand the pathogenesis of 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. All the following are good assessments of GA lesion enlargement EXCEPT

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

3. Which of the following is the No. 1 risk factor for advanced GA and AMD?

a. Age
b. Family History
c. Smoking History
d. Gender

4. You are seeing an 80-year-old patient with non-neovascular AMD in both eyes. You obtain fundus autofluorescence to better characterize her geographic atrophy. After obtaining this imaging, you unfortunately find that her pattern of GA puts her at increased risk of GA progression. What pattern of abnormal FAF did she likely demonstrate?

a. Normal
b. Patchy
c. Focal
d. Trickling

5. You are monitoring your 70-year-old patient with non-neovascular AMD in both eyes. You routinely obtain an OCT at each visit. All the following OCT features are associated with increased risk of faster GA progression EXCEPT:

a. Subretinal drusenoid deposits (SDD)
b. Intraretinal hyperreflective foci
c. Increased drusen volume
d. Hyporeflective foci within drusenoid lesions

6. What is the prevalence of wet and dry AMD in the United States?

a. 5 million
b. 11 million
c. 22 million
d. 33 million

7. GA is responsible for approximately what precentage of all cases of legal blindness?

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

8. Increased areas of hyperfluorescence on fundus autofluorescence are associated with _____.

a. Decreased lipofuscin accumulation which precedes development of GA
b. Decreased lipofuscin accumulation which coincides with development of GA
c. Increased lipofuscin accumulation which precedes development of GA
d. Increased lipofuscin accumulation which coincides with development of GA

PLEASE COMPLETE PRIOR TO ACCESSING THE MATERIAL AND SUBMIT WITH POSTTEST/ACTIVITY EVALUATION/SATISFACTION MEASURES INSTRUCTIONS FOR CE/CME CREDIT.

9. Which of the following imaging modalities is considered the gold standard for imaging GA patients?
a. FAF
b. OCT
c. B-scan ultrasonography
d. Color fundus photography

10. According to one study, how much does the presence of reticular pseudodresen increase a patients risk of progression of GA?
a. Two-fold increased risk
b. Three-fold increased risk
c. Four-fold increased risk
d. Five-fold increased risk

11. What is a key finding of GA on OCT?
a. Retinal thickening
b. Increased signal transmission below the RPE
c. Cystic intraretinal fluid
d. Intraretinal hyperreflective material

12. Lampalizumab is a drug under investigation for the treatment of GA through modification of:
a. The complement cascade
b. Mitochondrial activity
c. DNA transcription
d. Ribosomal activity

13. Phase 2 trials of monthly intravitreal pegcetacoplan have shown what rate in reduction of GA in enrolled patients compared to sham?
a. 19% reduction in GA
b. 29% reduction in GA
c. 39% reduction in GA
d. 49% reduction in GA

14. All of the following factors play a role in the development of GA EXCEPT:
a. Diet
b. Lifestyle
c. Smoking
d. Cataract status

15. Patients with which of the following characteristic of GA on FAF are most likely to experience disease progression?
a. Small lesions
b. Unifocal lesions
c. Banded lesions with hyperautofluorescent band surrounding the lesion margin
d. Banded lesions with hypoautofluorescent band surrounding the lesion margin

Geographic Atrophy: Best Practices for Diagnosis & Referral

Advanced age-related macular degeneration (AMD) is subtyped into exudative (also called "wet AMD") and nonexudative (also called "dry AMD") disease.[1] The prevalence of wet and dry AMD is estimated to be 11 million in the United States and 170 million globally.[2] Approximately 85 to 90% of patients with AMD have dry AMD.[3]

Historically, patients with advanced dry AMD present with geographic atrophy (GA) upon examination. GA was classically described as "a discrete area of retinal depigmentation at least 175 µm in diameter with a sharp border and visible choroidal vessels."[4] With advanced imaging modalities in 2021, however, GA can be detected earlier than when these classic findings show up on examination. GA may lead to central scotomas and loss of visual acuity,[5] and it has been shown that 31% of eyes with GA lose 3 lines of vision within 2 years, and that 53% of eyes lose 3 lines within 4 years.[6] The estimated prevalence of AMD in the United States was nearly 3 million for 2020.[7]

There is no treatment approved by the US FDA that halts or reverses GA and its effects. Drugs in the pipeline that are designed to address GA progression show some promise, but as of mid-2021, no complete set of pivotal trial data have found that any treatment is safe and effective for the treatment of GA. Eye care providers should stay abreast of the latest developments in GA therapy so that, if and when treatments are approved by regulatory agencies, they can knowledgably refer their patients to the proper channels to receive the latest care.

— Roger Goldberg, MD, MBA, Moderator

THE STATE OF GA IN 2021

Q | Roger Goldberg, MD, MBA: It is estimated that 3 million Americans have AMD, which is a significant increase from the 1.75 million Americans who were estimated to have it in 2004.[7] A partnership between optometrists and general ophthalmologists (who are most likely to detect evidence of GA in patients during routine and symptom-based eye exams) and retina specialists (who will be tasked with administering therapy to patients if and when such therapies are found safe and effective) will be key to ensuring that patients are properly referred and cared for. I'm curious to hear about the panel's experience with real-world GA patients. Do the prevalence numbers above match your perceptions?

David Lally, MD: I roughly see 15 to 20 patients every day with the presence of GA in at least one eye. Many of those eyes have concomitant neovascular disease. However, many are referred to my practice for consideration of a GA clinical trial. These high patient volumes underscore the prevalence of GA in the population that I treat.

Mary Beth Yackey, OD: Optometrists and general ophthalmologists see a large portion of the population with GA, perhaps because retina specialists have been inundated with patients seeking therapy for wet AMD, which has FDA-approved treatments. As of 2020, 26% of patients with bilateral GA were under the management of an optometrist or a general ophthalmologist.[8]

Dr. Goldberg: As a clinician, can you get a sense of how GA affects patients' lives?

Dr. Yackey: GA can have an immense effect on a patient's independence. Daily tasks such driving, meal preparation, reading, computer use, and shopping are all negatively affected by GA.[9] The literature has shown that depression rates are significantly higher in patients with GA compared with patients who do not have it, which should be cause for concern.[10]

Diana Shechtman, OD, FAAO: As someone who practices in South Florida, I see many older patients whose ability to drive has been affected by GA. It should be noted that society shares the burdens of GA in this way, too, as unsafe driving affects people beyond the patient. GA is responsible for approximately 20% of all cases of legal blindness,[11] which greatly affects the patient's activities of daily living.

As eye care provides become better equipped to detect—and potentially treat, in the future—GA, patient education remains key. In many cases, my patients are not aware of the early symptoms associated with GA. They have 20/20 BCVA and yet trouble with contrast sensitivity, which may affect their daily activities. Most may not feel a need to get an evaluation for minor visual disturbance and wait until there is apparent visual impairment. Unfortunately, that level of visual impairment is often associated with more advanced stages of disease.

Dr. Goldberg: I am regularly surprised by the disconnect between measured visual acuity and real-world functional vision in patients with GA. Patients might present with 20/20 BCVA, such as those described by Dr. Shechtman, but complain of reading difficulty or challenges when emerging from a tunnel while driving. In those patients, I look for evidence of GA. Other patients, however, are reluctant to tell me about changes to their functional vision. They chalk it up to having "old eyes." Detecting GA based on symptomatology alone, therefore, can be a challenge. The BCVA that we measure in a dark room with black letters on a white wall doesn't tell the full story, and we need to remember that when examining our patients.

Carlos Medina, MD: The foveal-sparing nature of early GA likely explains why some patients experience reduced visual function but normal Snellen BCVA measurements in our clinics. Indeed, real-world data have shown that patients with extrafoveal GA lesions have better vision than patients with foveal-involving GA lesions.[8] Still, it has been shown that BCVA and lesion enlargement are not necessarily correlated. These data illustrate the unique dynamic between anatomy and function in patients with GA.[12] In that sense, BCVA testing in inadequate.

Dr. Shechtman: Some of the patients who have been referred to our clinic with GA come with a note from the referring clinician in which they express concern about the patient's declining BCVA. Educating our referral network is critical. We may be able do more for a patient with 20/20 BCVA and early signs of GA than we can for a GA patient whose disease has already progressed. This will be especially crucial as new therapeutic treatment options become available, which can decrease progression of the disease.

Dr. Medina: Tests that evaluate functional vision rather than BCVA may prove useful in detecting and monitoring disease. Low luminance visual acuity (LLVA) testing may be more appropriate in patients with GA and good BCVA. It has been observed that LLVA is a more sensitive measurement than BCVA for assessing risk of visual decline.[13] Reading speed, which has been shown to correlate with GA lesion size, is useful for assessing a patient's ability to read full sentences rather than a single letter in the center of the visual field.[14] Patient questionnaires are also useful in this population, as they provide insight into how GA affects a patient's quality of life.[15] One such questionnaire, which was developed specifically for patients with GA, has been endorsed by the European Medicines Agency for use in clinical trials.[15] Like reading speed rates, scores on these questionnaires have been shown to correlate with GA lesion size.[16] Whether these tests fit in the workflow of a busy clinic is a different question, of course. In many instances, they do not.

Dr. Yackey: Dr. Medina is correct to note that some of these tests are too cumbersome for real-world high-volume clinics.

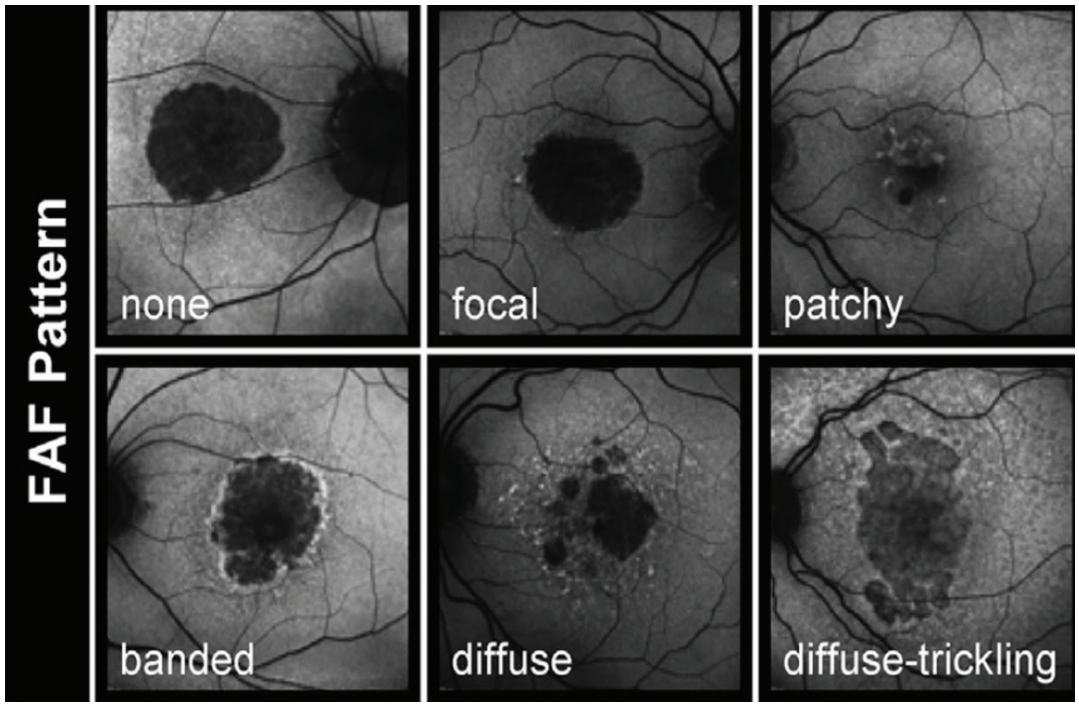

Figure 1. GA lesions as detected on FAF may be classified as focal, patchy, banded, diffuse, diffuse-trickling, or as having no pattern. Banded and diffuse lesions are the most likely lesions to progress.

Part of the benefit of such testing is that it can objectively show the patient that their visual function is declining even while their BCVA remains good. I have found that imaging reports work as an effective educational tool. By sharing the results of a fundus autofluorescence (FAF) scan, I can show a patient (and any family who has joined them) the presence of an extrafoveal macular lesion and explain how it will negatively affect their vision as the lesion progresses. Some patients understandably struggle to reconcile their good BCVA measurements with a prognosis of visual decline. After the patient sees an image of the macular lesion in their own eye , however, they begin to understand how progression of the disease will affect their vision.

Dr. Goldberg: Fitting GA examinations—and particularly some of these other functional tests such as LLVA and reading speed—into our workflow in an efficient way is key to maximizing the care we provide for our patient populations. Walk me through an appointment for a GA referral. (*See sidebar "The Value of Multimodal Imaging in Detecting New Geographic Atrophy" for a case depicting a new GA patient.*)

Dr. Medina: Every patient who comes into our clinic, regardless of the disease they are referred for, receives an OCT evaluation. Patients who are GA suspects also receive FAF imaging by our technicians at this point in the visit. By the time I see that patient, I have reviewed their OCT and FAF scans and am prepared for a thorough examination.

Dr. Shechtman: I follow a protocol similar to the one described by Dr. Medina. I find that FAF is a highly sensitive test, as it helps visualize the entire GA lesion area. It should be noted that increased areas of hyperfluorescence on FAF are associated with lipofuscin accumulation, which precedes development of GA. In the literature, FAF has been called the gold standard for imaging GA patients.[17]

Q | Dr. Goldberg: Large optometric clinics with greater resources may have access to imaging platforms such as FAF and OCT, but smaller clinics may not have them. Still, these practices will see patients with possible GA. How should they proceed with an examination?

Dr. Shechtman: In my experience, many optometrists in South Florida do not have OCT imaging. The chief reasons are twofold: the up-front cost of an OCT platform is high, and vision insurance plans do not reimburse for OCT imaging. Most of these practices do, however, have access to color fundus photography (CFP), which has been used in a number of studies to visualize GA lesions.[18,19] Although CFP is not as sensitive as OCT or FAF in detecting GA lesions, it can help eye care providers detect structural alternations that could indicate the presence of GA.

Dr. Lally: I see value in CFP, and patients who visit my practice receive CFP in addition to spectral-domain OCT (SD-OCT) and FAF during their visit with the technician. All of these images serve as a baseline against which we can refer later. On SD-OCT, I usually look for the double-layer sign (DLS). Instances in which I see a DLS lead me to investigate for macular neovascularization, which can be observed in greater detail using OCT angiography (OCT-A). Patients with extrafoveal GA lesions and a subfoveal DLS undergo OCT-A imaging so that I can understand the degree of neovascularization occurring near the DLS and, from there, understand the likely prognosis of their disease.

Dr. Shechtman: We can't ignore the value of OCT when it comes to visualizing changes in the outer retina and retinal pigment epithelium (RPE) in GA patients. OCT of patients with GA often shows overall thinning on the retinal thickness map, with variable retinal alterations. A key finding is increased signal

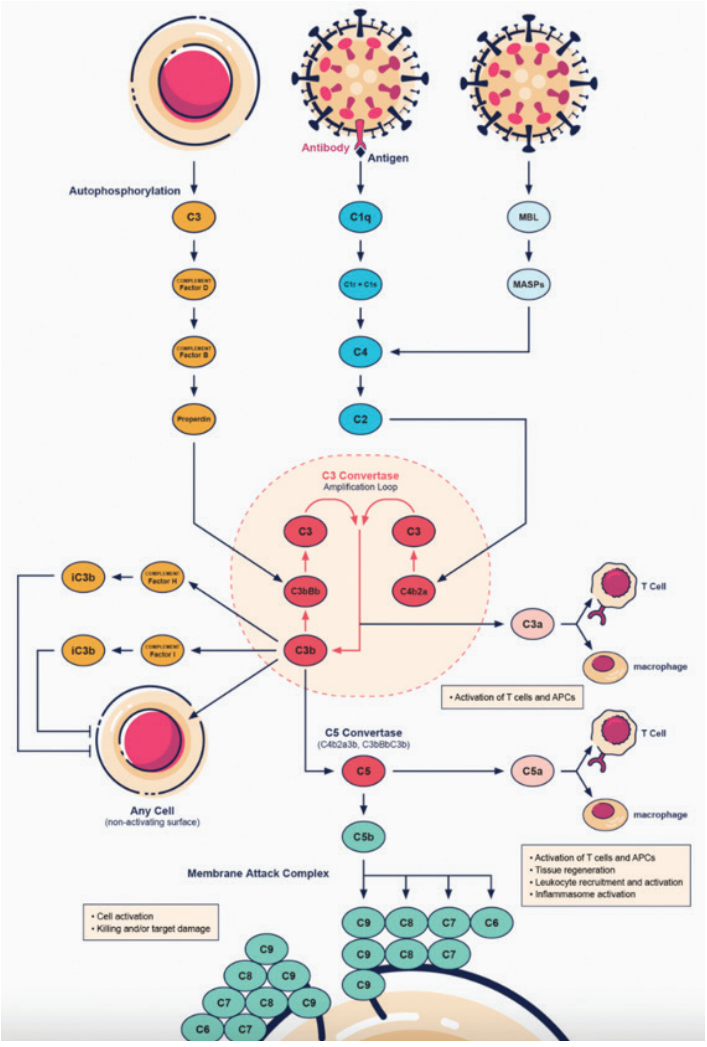

Figure 2. The classical, alternative, and lectin complement pathways all converge on C3. The cleavage of C3 results in the formation of C3b, which in turn leads to the activation of C5. When C5 is cleaved, C5b is formed, which combines with C6, C7, C8, and C9 to form MAC.

transmission below the RPE, associated with loss of the overlying retinal layers.

Dr. Goldberg: I agree with that wholeheartedly. Loss of the RPE overlying Bruch membrane, with secondary increased penetration into the choroid, is the hall mark finding of GA on OCT.[20] This can sometimes cause a "striping" on OCT that is easy for clinicians to recognize. This can also be useful for detecting the earliest forms of atrophy. Sadda et al determined that incomplete RPE and outer retinal atrophy (iRORA) and complete RORA (cRORA) are two nascent forms of GA, with iRORA progressing to cRORA.[21] Using their paradigm could allow disease detection in patients with very early GA—who are, to the point Dr. Shechtman made earlier, the patients we will most be able to help whenever the FDA approves a treatment for GA.

Research has found that GA lesions detected on FAF can be categorized based on their shape, pattern, and/or hyperautofluorescence at the lesion border (Figure 1). Bindewald et al found that small lesions and unifocal lesions progress slower than large or multifocal lesions,[22] and Hu et al have found that patients with banded lesions (ie, those with a hyperautofluorescent band surrounding the lesion margin) and autofluorescence changes beyond the lesion border are most likely to experience disease progression.[23] These categorizations are useful for clinicians, but I wonder how much utility they have for explaining likely disease progression to patients.

Dr. Medina: I don't go into much detail regarding focality or lesion band patterns during my discussion with patients. I might speak in general terms, such as telling the patient that bigger lesions grow more quickly. And if I have baseline images against which to compare their most recent image, I may use that to illustrate lesion growth. Anything beyond that, though, functions only to confuse or depress the patient about their eventual visual decline.

The only circumstances in which I get into details about the relationship between focality/lesion type and disease progression is if I'm talking to a patient about enrolling in a clinical trial or if I'm preparing for a discussion about risk factor modification, such as smoking cessation or diet adjustments.

Dr. Lally: For the most part, patients with GA know that they have a visual problem. Until we have an FDA-approved treatment for GA, one of the most helpful discussions we can have with these patients is to prepare them for activities of daily living which may need adjusted in the coming years. Conversations with patients about their specific visual needs are key. Are they currently driving? Do they take care of an aging spouse? Do they read or cook or use a checkbook? When we have answers to these types of questions along with an understanding of disease progression based on the lesion characteristics, then we can provide guidance for patients about how the visual changes they may experience in the forthcoming year will affect the most important aspects of their lives.

Dr. Goldberg: Whenever we do get an FDA-approved therapy for GA, the conversation around lesion location and types will be different. At that point, we can use those data to gauge which patients are best suited for therapy. Until that occurs, however, we chiefly use these images to determine the rate of progression.

Dr. Yackey: Discussing the promise of the GA pipeline with some patients is appropriate, as long as it is done ethically. For patients who present with lesions that are less likely to rapidly progress—that is, smaller lesions, nonbanded lesions, and unifocal lesions—we consider telling them that some drugs are under investigation to treat their disease. We need to balance educating our patients against inspiring false hope.

Dr. Shechtman: If clinical findings and ancillary imaging tests suggest that the patients is likely to progress slowly, my

follow-up regimen of 6 to 12 months. If, however, there is evidence that the patient may progress quickly, I tend to follow that patient closely, and consider asking them to return within 3 to 6 months.

Dr. Medina: My practice pattern is similar. Sometimes these patients are good candidates for a clinical trial, or are just on the cusp of the enrollment criteria. In those cases, I ask the patient to return sooner than they normally might. In other instances, if I sense that a patient might soon develop a DSL or advance to foveal-involving disease, I ask them to return in a 3- to 6-month window. I also ask patients to return in an earlier window if I observe reticular pseudodrusen (RPD) on examination. Multiple studies have linked the presence of RPD to the progression of GA,[24-28] with one study showing that the risk of progression was nearly 5 times higher for patients with RPD.[24]

Q | Dr. Goldberg: When it comes to optometry and general ophthalmology, some clinicians may not see a value in referring to a retina specialist because there is no FDA-approved therapy. Do you feel there is value in a patient seeing a retina specialist despite the fact that there is little we can do to treat their condition at the moment?

Dr. Lally: Getting GA patients on the radar of retina specialists is going to be important to ensuring that treatment—if and when it becomes available—can be administered promptly. I encourage the optometrists and general ophthalmologists with whom I collaborate to have a low threshold for referral. If any GA lesions are detected, I think referral is appropriate. Keep in mind that some patients progress very quickly. Functional vision could deteriorate in the period between semiannual or annual eye examinations, so the sooner a retina specialist sees these patients, the better.

PATHOGENESIS OF GA AND THE ROLE OF THE COMPLEMENT SYSTEM

Q | Dr. Goldberg: Controllable and uncontrollable nonophthalmic factors contribute to GA risk. What are some of the risk factors that are linked to GA development or progression that you often consider?

Dr. Yackey: As might be expected with an age-based disease, age is a major risk factor for the development of GA. The Beaver Dam Eye Study, a population-based cohort study, found that 3.2% of patients who were at least 75 years old had GA, compared with 0.0% of patients who were under 54 years old.[29] A family history of AMD is also a risk factor for the development of GA.[30]

Genetics also play a role in a patient's risk for developing GA. Patients who have both risk alleles CFH and ARMS2 are at increased risk for developing AMD.[31] Specific to GA development, the presence of CFH variant Y402H increases a patient's risk of developing GA independent of smoking status.[32]

Dr. Medina: Diet, lifestyle, and smoking all play a role in development of GA,[30,33] and I encourage patients to address these controllable factors whenever possible. Current smoking status in particular is a major factor, as risk of developing advanced AMD has been linked to current smoking status.[31] But for many of our patients, treatments will likely have a more profound effect than adjusting the above factors. Luckily, data from several clinical trials give us hope that a treatment may soon be approved by regulatory bodies.

Dr. Goldberg: Our knowledge of the pathology of GA has improved as research has become more robust in the past several years, leading researchers to conclude that compliment disruption might be linked to the development of GA. Indeed, data such as that published by Ambati et al found that drusen in GA patients contains complement components C1q, C3, C5, and C3b-9, implicating the complement cascade in the pathogenesis of GA.[34]

Let's break down the complement system and the complement cascade so that we can further understand the biologic mechanisms behind GA development and growth.

Dr. Lally: The complement system is part of the innate immune system. It contains three main pathways: the classical pathway, the lectin pathway, and the alternative pathway.[35] The activation of each pathway ultimately can result in cell death. When functioning properly, such cell death is directed at foreign bodies. However, in the case of GA, complement disruption may lead to the death of cells in the retina itself.

All three pathways converge on complement component 3, often simply called C3 (Figure 2). In the alternative pathway, C3 cleaves into C3a and C3b, which contributes to cell death and C5 activation.[35] The alternative pathway is activated in part by complement factor D (CFD).[37] Further down the cascade, C5 convertase cleaves C5, leading to the creation of C5b, which combines with C6, C7, C8, and C9 to create membrane attack complex (MAC),[38] a protein complex that attacks cells.

Given the multiple points at which we could intervene in the complement cascade and the findings that the drusen deposits contain complement components, complement inhibition has been the main focus of pipeline development.

Dr. Goldberg: A return to this level of basic science may surprise some clinicians, but it's important to have a working understanding of the biologic mechanisms that may be activating this devastating disease. Plus, when we understand the complement system's role in disease activity, we can better understand mechanisms of action of potential therapies targeting the complement cascade.

THE GA PIPELINE

Dr. Goldberg: A number of drug candidates have been evaluated for the treatment of GA, several of which leverage the opportunities presented by the complement cascade. Let's review some of the top-line data from some of the most important trials in GA therapy.

THE VALUE OF MULTIMODAL IMAGING IN DETECTING NEW GEOGRAPHIC ATROPHY

By Roger Goldberg, MD, MBA

A 69-year-old white man presented to my clinic with complaints of difficult night driving and reduced contrast sensitivity. A clinical exam revealed 20/40 VA OU and trace nuclear sclerosis. Diffuse drusen were detected, but there was no evidence of geographic atrophy (GA) lesions on exam or on color fundus photography (CFP; Figure 1).

The patient underwent fundus autofluorescence (FAF) and OCT imaging. On FAF, multifocal GA lesions were present OU (Figure 1). OCT imaging showed atrophy of the retinal pigment epithelium (RPE) that is characteristic of GA, with increased transmission into the choroid (Figure 2).

This case demonstrates that multimodal imaging of GA patients is valuable in the assessment of new patients. If this patient had only undergone routine examination and monomodal imaging (ie, CFP), no GA lesions would have been detected. Instead, lesions were detected, and cross-sectional imaging confirmed patterns of atrophy in the RPE.

Although FAF may be gold standard platform for GA imaging, not all practices keep this modality in house. Practices that have access only to CFP should consider referring any GA suspects to a practice with multimodal imaging capacity. Clinicians with OCT may choose to rely on evidence of RPE atrophy by detecting increased transmission into choroid to diagnose GA.

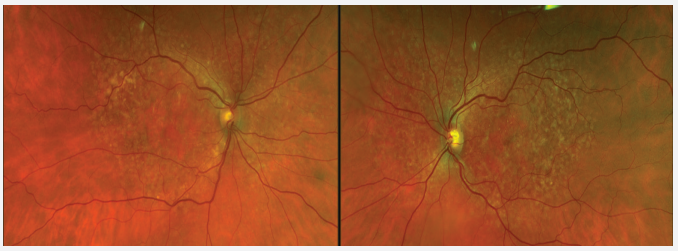

Figure 1. Bilateral CFP revealed evidence of drusen but no GA lesions.

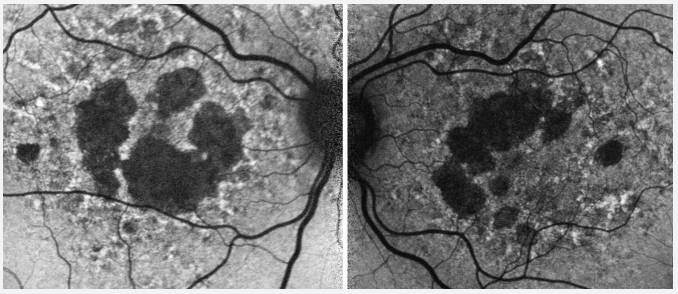

Figure 2. On FAF, multifocal GA lesions were observed in both eyes.

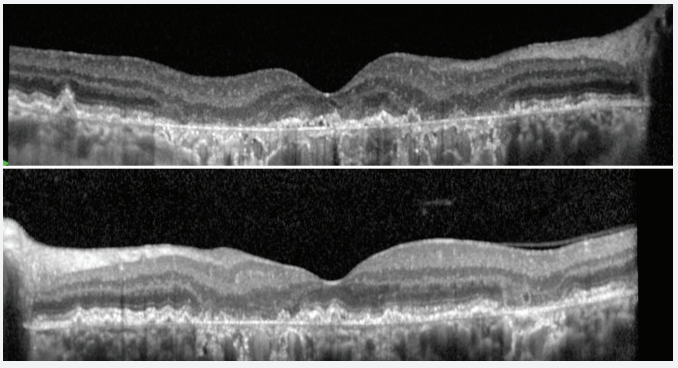

Figure 3. Atrophy of the RPE and increased transmission into the choroid were observed on OCT.

Dr. Lally: Earlier, I explained that CFD activated the alternative pathway.[37] Lampalizumab is a CFD inhibitor that was evaluated in the phase 3 Chroma and Spectri trials.[39] Researchers enrolled patients with bilateral GA and randomly assigned them to receive 10 mg lampalizumab every 4 or 6 weeks, or sham every 4 to 6 weeks. The study's primary endpoint was mean change of GA lesion area from baseline at week 48. It was determined that patients in the treatment arms did not demonstrate a reduction in GA enlargement compared with patients in the sham groups.

Dr. Goldberg: The inability of lampalizumab to significantly reduce GA lesion growth area was discouraging news for the eye care community—particularly among those who envisioned the complement cascade as a viable target for complement inhibition—but other drugs have seen success in phase 2 and phase 3.

Dr. Lally: The two drugs to which Dr. Goldberg is referring—pegcetacoplan and avacincaptad pegol—are PEGylated. PEGylation may increase retention and slow down metabolism,

which could give these drugs some advantages over lampalizumab, which was not PEGylated.

Dr. Goldberg: Let's talk about those two drugs now. Dr. Shechtman, before I review pegcetacoplan, can you update us on the status of avacincaptad pegol?

Dr. Shechtman: Avacincaptad pegol is a C5 inhibitor that aims to disrupt the formation of MAC.[40,41] The study's two pivotal trials are titled GATHER1 and GATHER2. In the GATHER1 study, researchers enrolled patients with GA secondary to dry AMD and randomly assigned them to receive monthly 2 mg or 4 mg of intravitreal avacincaptad pegol or sham. Patients in both treatment arms demonstrated a significantly improved reduction in the mean rate of GA growth area at 1 year, with reductions of 27.4% (P = .007) and 27.8% (P = .005) in the 2-mg and 4-mg groups, respectively.

The GATHER2 study is expected to complete its enrollment of 400 patients by the end of July 2021.[42] In that study, patients will be randomly assigned to monthly treatment or sham, and the mean rate of change of GA growth during a 12-month period will remain the primary endpoint.[43] At month 12, patients in the treatment arm will be randomly assigned to receive monthly or every-other-month (EOM) treatment, with final data readouts occurring at the end of year 2.[43]

Dr. Goldberg: Pegcetacoplan is a C3 inhibitor, which targets a mechanism further upstream in the complement cascade. C3 is the convergence point of the three complement pathways, and inhibition of C3 may prevent the cascade that allows C5 and other downstream elements to activate. Pegcetacoplan is also designed to bind to C3b, which leads both to cell death and the activation of C5.

In the phase 2 FILLY study, researchers enrolled patients with GA secondary to AMD and randomly assigned them to receive 15 mg intravitreal pegcetacoplan monthly or EOM or sham monthly or EOM.[44] A 29% and 20% reduction in the rate of GA lesion growth was observed at month 12 in patients who received monthly and EOM treatment, respectively.[44] Both of these reductions were considered statistically significant.[45] The phase 3 DERBY and OAKS studies will evaluate the safety and efficacy of pegcetacoplan in pivotal trials. Topline data from those studies are expected in the third quarter of 2021.[46]

Dr. Medina: A post-hoc analysis of the FILLY study assessed patients on FAF imaging. Patients with iRORA were 39% less likely to advance to cRORA,[47] which could mean that pegcetacoplan is appropriate for early intervention of patients with GA. Further studies on this topic are needed.

Dr. Lally: As long as we're talking about the complement pathway, we should mention the phase 2 HORIZON54 and EXPLORE55 trials, which are assessing the upregulation of complement factor I (CFI) for the treatment of GA secondary to dry AMD via the drug GT005 (Gyroscope Therapeutics). The studies have a novel approach insofar that they are grouping patients in the study by genotype. In fact, patients in the EXPLORE study will all have rare CFI gene variants.

Q | Dr. Goldberg: A number of therapies have targeted biological mechanisms other than the complement cascade. Have we seen success or momentum with any of those therapies?

Dr. Medina: Attempts to decrease toxic metabolic byproducts associated with retinal tissue function have not shown much success and have been associated with delayed dark adaption.

Such failures are not isolated in the GA pipeline. The C5 inhibitors eculizumab[48] (Solaris, Alexion Pharmaceuticals) and tesidolumab[49,50] (LFG316, Novartis) did not demonstrate reductions in GA lesion growth. That said, current clinical trials have shown some degree of promise, so we shouldn't be too certain that past failures will dictate future ones.

Dr. Yackey: The Cincinnati Eye Institute recently participated in a phase 1/2a study that explored the safety and efficacy of the subretinal transplantation of human embryonic stem cell–derived RPE cells for the treatment of GA.[51] The procedure was well tolerated, and encouraging structural and clinical changes were observed. As this is an early-stage study, I expect further research in this area.

Part of our job as eye care providers is to ensure that patients understand that clinical trials are never patient-funded ventures, and that any patient who is paying for cell therapy for GA should do so with extreme caution. In a 2019 study, Nirwan et al found a number of direct-to-consumer marketing campaigns that advertised cell therapy for GA,[52] leading Parke II to point out that the out-of-pocket nature of payment for these procedures occurred despite language such as "clinical trial" and "research" appearing in the marketing materials.[53]

Dr. Goldberg: That is such an important point. We need to ensure the safety of our patients, and part of our job is to caution patients that, if they seek second opinions, they must do so with legitimate, ethical clinics. If a supposed clinical trial is patient-funded, it is likely not a clinical trial at all.

We all hope that a therapy for GA will be approved in the near future, which will finally allow eye care providers to direct patients toward relief for their condition. Until that day comes, we must stay prepared and educated so that we can hit the ground running as soon as we are able to treat patients with GA. ■

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GEOGRAPHIC ATROPHY: BEST PRACTICES FOR DIAGNOSIS & REFERRAL

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CME Expiration Date: September 2022
COPE Expiration Date: August 6 2022

INSTRUCTIONS FOR CME CREDIT

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License Number _____ OE Tracker Number _____

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 activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss the prevalence of AMD	_____	_____	_____
Articulate the burden of illness linked to GA	_____	_____	_____
Understand the pathogenesis of GA	_____	_____	_____
Describe disease detection and factors influencing progression	_____	_____	_____
Review the therapeutic interventions that have been explored as well as those in the pipeline	_____	_____	_____

POSTTEST QUESTIONS

PLEASE COMPLETE AT THE CONCLUSION OF THE ACTIVITY.

1. Based on this activity, please rate your confidence in your ability to understand the pathogenesis of 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. All the following are good assessments of GA lesion enlargement EXCEPT
a. Microperimetry
b. Low-luminance VA
c. Reading speed assessments
d. Best corrected visual acuity

3. Which of the following is the No. 1 risk factor for advanced GA and AMD?
a. Age
b. Family History
c. Smoking History
d. Gender

4. You are seeing an 80-year-old patient with non-neovascular AMD in both eyes. You obtain fundus autofluorescence to better characterize her geographic atrophy. After obtaining this imaging, you unfortunately find that her pattern of GA puts her at increased risk of GA progression. What pattern of abnormal FAF did she likely demonstrate?
a. Normal
b. Patchy
c. Focal
d. Trickling

5. You are monitoring your 70-year-old patient with non-neovascular AMD in both eyes. You routinely obtain an OCT at each visit. All the following OCT features are associated with increased risk of faster GA progression EXCEPT:
a. Subretinal drusenoid deposits (SDD)
b. Intraretinal hyperreflective foci
c. Increased drusen volume
d. Hyporeflective foci within drusenoid lesions

6. What is the prevalence of wet and dry AMD in the United States?
a. 5 million
b. 11 million
c. 22 million
d. 33 million

7. GA is responsible for approximately what precentage of all cases of legal blindness?
a. 10%
b. 20%
c. 30%
d. 40%

8. Increased areas of hyperfluorescence on fundus autofluorescence are associated with _____.
a. Decreased lipofuscin accumulation which precedes development of GA
b. Decreased lipofuscin accumulation which coincides with development of GA
c. Increased lipofuscin accumulation which precedes development of GA
d. Increased lipofuscin accumulation which coincides with development of GA

9. Which of the following imaging modalities is considered the gold standard for imaging GA patients?
a. FAF
b. OCT
c. B-scan ultrasonography
d. Color fundus photography

10. According to one study, how much does the presence of reticular pseudodresen increase a patients risk of progression of GA?
a. Two-fold increased risk
b. Three-fold increased risk
c. Four-fold increased risk
d. Five-fold increased risk

11. What is a key finding of GA on OCT?
a. Retinal thickening
b. Increased signal transmission below the RPE
c. Cystic intraretinal fluid
d. Intraretinal hyperreflective material

12. Lampalizumab is a drug under investigation for the treatment of GA through modification of:
a. The complement cascade
b. Mitochondrial activity
c. DNA transcription
d. Ribosomal activity

13. Phase 2 trials of monthly intravitreal pegcetacoplan have shown what rate in reduction of GA in enrolled patients compared to sham?
a. 19% reduction in GA
b. 29% reduction in GA
c. 39% reduction in GA
d. 49% reduction in GA

14. All of the following factors play a role in the development of GA EXCEPT:
a. Diet
b. Lifestyle
c. Smoking
d. Cataract status

15. Patients with which of the following characteristic of GA on FAF are most likely to experience disease progression?
a. Small lesions
b. Unifocal lesions
c. Banded lesions with hyperautofluorescent band surrounding the lesion margin
d. Banded lesions with hypoautofluorescent band surrounding the lesion margin

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this CE/CME 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: _____ Yes _____ No _____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 diagnostic testing
_____ Change in current practice for referral
_____ My practice has been reinforced
_____ Change in nonpharmaceutical therapy
_____ Choice of treatment/management approach
_____ Change in differential diagnosis
_____ 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

Would you 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 CE/CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____

MODERN**OPTOMETRY**