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GEOGRAPHIC ATROPHY MANAGEMENT:

THE ROLE OF COMPLEMENT MODULATION-BASED THERAPIES

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Content Source

This continuing medical education (CME) activity captures content from a roundtable discussion.

Activity Description

This supplement summarizes a discussion on understanding clinical trial data on emerging and potential therapies for geographic atrophy and communicating with patients.

Target Audience

This certified CME activity is designed for retina specialists.

Learning Objectives

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

- **Review** updates in the classification for dry age-related macular degeneration, in particular the significance of incomplete retinal pigment epithelial and outer retinal atrophy (iRORA) and complete retinal pigment epithelial and outer retinal atrophy (cRORA)
- **Appraise** anatomical retinal features that may serve as biomarkers of geographic atrophy (GA) progression
- **Identify** lesion-specific factors that may predict treatment response
- **Describe** the role of the complement pathway in GA development and progression
- **Critique** clinical trial evidence for pipeline complement modulation-based therapies

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PRETEST QUESTIONS

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1. Please rate your confidence in your ability to manage patients with 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. Which of the following OCT features may serve as a biomarker that portends a higher risk of progression to GA?

a. Hyporeflective foci overlying drusen
b. Hyperreflective foci within drusen
c. Reticular pseudodrusen
d. Absence of drusen

3. All of the following represent good ways to determine functional vision in patients with age-related macular degeneration (AMD), EXCEPT:

a. Contrast sensitivity
b. Reading speed
c. Low luminance visual acuity
d. Snellen visual acuity

4. You are seeing a 78-year-old man with nonneovascular AMD. His GA has been progressing, and he is increasingly disturbed by his visual function. He is eager to seek therapy for his GA, but wonders about potential side effects. Which of the following statements about GA therapeutic side effects is true?

a. There is a significant risk of intraocular inflammation with GA therapies
b. There is a risk of the development of macular neovascularization with GA therapies
c. There is a high risk of endophthalmitis with GA therapies
d. There is a high risk of angle-closure glaucoma with GA therapies

5. An 80-year-old woman presents to your office for evaluation. Her BCVA is 20/100 OD and 20/80 OS. She has bilateral fovea-involving GA. Her fundus autofluorescence photos show a pattern of GA that is considered high risk in both eyes. Which of the following statements is the most reasonable option for this patient?

a. Do not consider GA therapy for this patient because her disease is bilateral and high risk
b. Do not consider GA therapy for this patient because her GA is fovea-involving
c. Consider GA therapy for this patient because her vision is midrange and in the context of the visual acuity included in GA therapy trials
d. Consider GA therapy for this patient but only in her left eye

6. An 80-year-old man with AMD presents to your office for evaluation. His OCT demonstrates a zone of retinal pigment epithelium (RPE) attenuation and choroidal hypertransmission 300 µm with overlying photoreceptor degeneration. Which of the following statements is true about this patient?

a. This patient has OCT evidence of incomplete RPE and outer retinal atrophy (iRORA) and has high risk of GA progression
b. This patient has OCT evidence of complete RPE and outer retinal atrophy (cRORA) and low risk of GA progression
c. This patient has OCT evidence of iRORA and low risk of GA progression
d. This patient has OCT evidence of cRORA and high risk of GA progression

Geographic Atrophy Management: The Role of Complement Modulation-Based Therapies

In the Western world, age-related macular degeneration (AMD) is the leading cause of vision loss in individuals aged 60 years and older.[1] Dry AMD accounts for approximately 90% of all patients with AMD, of which 20% develop advanced dry AMD or geographic atrophy (GA).[2] More than 5 million people are affected by GA worldwide, which is projected to increase to more than 10 million people by 2040.[3]

The year 2023 is proving to be a turning point in the treatment of GA. The FDA approval of pegcetacoplan on February 17th is the most important advance in retina care since the introduction of anti-VEGF pharmacotherapies. This is a breath of fresh air, with hopefully more to come as there are numerous differentiated therapeutics with unique mechanisms of action in clinical trials, including avacincaptad pegol which has an expected approval date of August 19, 2023. In this context, many remain uncertain of how best to interpret the trial data supporting FDA approval of pegcetacoplan and how best to serve their patients with this new therapeutic.

This supplement, based on a roundtable that took place prior to the approval of pegcetacoplan, features a fantastic group of colleagues discussing how the field is likely going to move forward and, importantly, how to consider discussing disease progression and treatment considerations with patients.

—Charles C. Wykoff, MD, PhD, Program Chair

DEALING WITH THE RISK OF PROGRESSION

Q | Dr. Wykoff: What do you currently communicate to patients with intermediate AMD about the advanced stages of AMD?

Mrinali Gupta, MD: I begin by noting that dry AMD is the most common form and, generally, progresses slowly. The advanced stages can manifest in one of two ways, and both significantly impact vision. One is the conversion to the wet form of AMD, neovascular AMD (nAMD). Fortunately, we have effective treatments that help maintain vision if nAMD is detected early and treated appropriately. The other form of advanced AMD is GA. As intermediate AMD progresses, there may be a gradual decline in vision, but progression to GA can hasten vision loss. I explain that atrophy equates to tissue loss, meaning it cannot be recovered. If it occurs in the noncentral parts of the retina, patients may notice vision impairment such as difficulty reading, especially in dim light. However, if atrophy occurs in the central retina, they can lose central vision.

Dr. Wykoff: There are several therapeutics in the pipeline aiming to treat GA, but we hope to one day have treatments that can be administered at the intermediate AMD stage. OCT has been used to identify biomarkers in intermediate AMD that portend a higher risk for progression to GA, eg, hyperreflective foci overlying drusen, hyporeflective foci within drusen, reticular pseudodrusen, and drusen volume. Do you look for these biomarkers in patients with intermediate AMD and stratify their risk for progression?

Dr. Gupta: I do. Sometimes I can see the evolution of certain high-risk features, ie, retinal pigment epithelial (RPE) disruption and hyperreflectivity, and loss of definition in the outer retina, as the patient develops atrophy or as atrophy grows. I don't go into detail about these with patients. Instead, I focus on the modifiable and nonmodifiable risk factors for AMD, which are easier to understand and actionable for patients.

Jayanth Sridhar, MD: We certainly talk a lot about imaging biomarkers at meetings. The Classification of Atrophy Meetings (CAM) have published consensus terminology and criteria for defining atrophy based on OCT findings.[4] For example, atrophy regardless of the presence or absence of neovascularization is termed complete RPE and outer retinal atrophy (cRORA), and is defined by a zone of choroidal hypertransmission of at least 250 µm, RPE attenuation of at least 250 µm, and corresponding region of overlying photoreceptor degeneration in the absence of an RPE tear or scrolled RPE. However, I suspect most of us don't look at imaging biomarkers or use OCT-defined terminology for atrophy in clinical practice. In fact, we spend more time looking for risk factors for nAMD, even using OCT-angiography (OCTA) to screen for nonpathologic macular neovascularization (MNV). We spend less time focusing on precursors to GA, like incomplete RPE and outer retinal atrophy (iRORA)

because, historically, we couldn't do much about it. When we have a treatment for GA, we'll likely better educate ourselves on risk factors, new terminology, and treatment criteria.

Q | Dr. Wykoff: What do you currently communicate to patients with nAMD about their risk for developing atrophy over time?

Dr. Sridhar: Most of the conversation around AMD is setting expectations. Patients are often worried about vision loss, so I explain that only a small percentage progress to advanced AMD, either nAMD or GA. Truthfully, I spend more time educating patients about the conversion to nAMD in the fellow eye than the progression of nAMD to GA, but I do mention it. Certainly, if I see signs of developing atrophy, I prepare patients and accompanying caregivers for the road ahead. This may be another aspect of GA that receives more airtime once therapies are available.

Dr. Gupta: This conversation comes up most often with patients who have well-controlled nAMD, ie, no fluid or heme, but they're losing vision. This is when I reiterate that AMD has a dry component and that treating nAMD doesn't necessarily prevent the dry component or atrophy from progressing in parallel.

Geeta Lalwani, MD: Whether in the absence or presence of MNV, GA will require more time-consuming patient education.

Q | Dr. Wykoff: What do you currently communicate to your patients with GA about the disease?

Dr. Lalwani: I qualify GA progression using OCT and fundus autofluorescence (FAF) images. I then categorize patients by their visual acuity. For patients who have poor visual acuity, I focus on safety. We talk about driving and support with certain activities at home. I avoid telling them what they should do. Instead, I help them understand their limitations. We talk about lifestyle modifications and what they could do to ensure safety. I try not to use the "b word" because no one wants to be told that they're blind.

It's harder to explain the possibility of poor functional vision due to progressive extrafoveal lesions to patients who currently have good visual acuity. I start by conceding that the Snellen chart is the fastest and most objective way to measure visual acuity but isn't ideal for assessing the full spectrum of visual deficits. When I mention decreased contrast sensitivity, reading speed, and the need for better lighting, they begin to open up and admit that they are already struggling with these symptoms.

Q | Dr. Wykoff: What are the specific complaints you hear from patients with extrafoveal lesions?

Dr. Lalwani: They talk about missing words or words jumping around when reading. They sometimes complain about dark areas on one side or the other. They complain that they feel like their vision is worsening, even if our clinic obtains the same visual acuity from visit to visit.

"The first thing I do for patients with central GA and 20/200 VA is refer them to low vision specialists to help them make the most of their vision."

—Mrinali Gupta, MD

Anton Orlin, MD: The severity of the visual compromise depends on the extent of GA. Many patients have 20/20 VA but are asymptomatic and have varying degrees of trouble reading, driving, and seeing at night.

Dr. Gupta: The first thing I do for patients with central GA and 20/200 VA is refer them to low vision specialists to help them make the most of their vision. Even patients with good visual acuity who complain about functional vision deficits could benefit from a referral.

Q | Dr. Wykoff: Many retina specialists are hesitant to initiate that conversation because they don't want to overpromise the utility of low vision aids. How do you have that conversation?

Dr. Gupta: I typically explain that low vision specialists can provide something as simple as a pair of glasses, lights, magnifiers, and devices to help make the most of the vision they currently have.

Dr. Lalwani: If you have a very good low vision specialist in your area, that's great, but otherwise I'd be wary of the referral. These patients want to see well. They're a very vulnerable population. I always tell them, "The moon is not for sale, please don't go out and buy it. Your vision is not coming back."

Dr. Wykoff: I take the same approach. I encourage the referral, but counsel them not to buy anything too quickly and, if they can, make sure it has a good return policy. I've had patients be disappointed after buying devices that don't work for them.

Dr. Sridhar: It all stems from this lack of correlation between visual acuity and function. I make sure patients understand this disconnect. Often, they don't feel validated by the visual acuity chart, especially in front of caregivers who may think that their complaints about vision are unfounded. I describe that they're relying on a square millimeter or so of central vision. A single letter on the Snellen chart fits into this area but a longer sentence won't. Hence, reading becomes more challenging. Some patients

feel much better after they understand this.

The other important point to communicate is that when there is foveal involvement, visual acuity loss can occur rapidly. A recent study using data from the Intelligent Research in Sight registry found that the mean annual probability of progression from 20/63 VA or better to 20/400 VA or worse was almost 10-fold higher in eyes with GA subfoveal involvement versus eyes with mild dry AMD.[5] Patients with GA without subfoveal loss saw an average annual visual acuity loss of 3.9 letters. Referencing such studies can be helpful when describing what patients can expect in terms of visual acuity loss.[5]

Q | Dr. Wykoff: Given this disconnect between anatomy and function, we do have additional tools that assess visual function, eg, microperimetry and contrast sensitivity testing. Do you use these or other functional tests clinically? If not, what would it take for us to begin using more metrics of visual function?

Dr. Sridhar: Most physicians don't use these tests, particularly microperimetry, in clinical practice. Tests need to be reproducible and fit easily within practice flow, eg, Snellen visual acuity testing. If microperimetry technology evolved to the point of being like OCT, ie, easy to perform and generates a relatively easily interpretable result in-office, it would be more widely adopted. However, the current technology does not seem to provide reliability and efficiency.

Dr. Lalwani: Time is a major limiting factor in our busy retina clinics. Once a therapy is available, the next challenge will be to determine ideal patient candidates. Baseline tests such as low luminescence reading and microperimetry may play a role, but it's been suggested that partnering with other eye care colleagues could ease this testing burden and better screen patients.

Dr. Gupta: We haven't previously needed functional testing because we haven't had any treatments that relied on assessing vision in those ways. We treated based on anatomic features such as subretinal fluid. If these GA drugs are approved, we'll need other ways of monitoring patients to gauge treatment response.

Dr. Wykoff: Some OCT systems have software that measures GA area. However, it's not automated and it's time-consuming. An ideal scenario would be something akin to retinal nerve fiber layer measurements that track progression. Do any of you currently track GA area in your clinical patients?

Dr. Sridhar: I don't, but I plan to after therapies are available. Unlike nAMD, in which the decision to treat is binary, ie, is there exudation or not, GA therapies slow progression of atrophy. In an ideal world, we'd have algorithms that generate a natural history of disease progression for each patient showing how treatment had slowed that progression. Unfortunately, until we have functional studies with easy, in-office technology that can show improvements correlated with these treatments, patients with GA won't see and be encouraged by the "wow" effect of treatment that patients with nAMD or diabetic eye disease see on OCT and with visual acuity. If we can't somehow show that treatment is working, it'll be difficult for both patients and physicians to adhere to treatment.

KEY LEARNINGS FROM RECENT CLINICAL TRIALS FOR GA THERAPIES

Q | Dr. Wykoff: Are you talking with patients about GA therapies on the horizon?

Dr. Orlin: Now, I am. In the past, we'd tell patients that we couldn't offer effective treatment for their disease. We could only monitor them every 4 to 6 months. It's very exciting that we could soon have two GA treatments. I introduce the topic by discussing the drugs and promising trial results. We are seeing a decreased rate of GA progression with a similar safety profile to anti-VEGF intravitreal injections. The FDA is still reviewing the data, but these drugs could be available soon.

Dr. Wykoff: How do you tackle the issues related to vision with these drugs? Most patients equate therapy to vision gain, even if they don't voice it.

Dr. Orlin: I give them realistic expectations that the drug could prevent further vision loss as opposed to gaining back vision. How patients receive this information depends on the extent of their clinical findings. If they've already lost considerable vision in one eye, they are very excited that we could slow down or prevent similar problems in the fellow eye. Patients who are in the earlier stages of disease and relatively asymptomatic may initially be less excited.

Dr. Sridhar: I hit on three main points in these conversations: they're intravitreal injections, they'll be life-long because there is no endpoint at which treatment can be stopped, and they slow disease progression not return lost vision. It's important not to overpromise, especially with patients that have significant atrophy who continue to ask us how to get their vision back.

Q | Dr. Wykoff: Both pegcetacoplan and avacincaptad pegol have phase 3 trial data. What have we learned from these data to date?

Dr. Sridhar: They both inhibit the complement pathway, which has been heavily implicated in AMD in genetic and histopathological studies.[6-8] The pathway has previously received a lot of interest in AMD. Unfortunately, other complement inhibitors have failed in clinical trials.[9-11] What's exciting about pegcetacoplan and avacincaptad pegol is that the results are encouraging. The 2-year DERBY and OAKS phase 3 trials for pegcetacoplan and 1 year GATHER-2 phase 3 trial for avacincaptad pegol showed statistically significant reduction in lesion growth over time.[12,13] It wasn't a dramatic reduction; depending on the trial, the percentage ranged from the high teens to low thirties, compared to sham.[12,13] Notably,

patients did still progress, but its promising that the treatment effect for pegcetacoplan increased with time.[12] That may be why the trial sponsor decided to submit the 2-year data and push back the target date for FDA approval from November 2022 to February 2023.[14]

Dr. Lalwani: It's been interesting to see how the baseline criteria have influenced treatment response measurements. We've known that FAF pattern, lesion size, junctional zone abnormalities, and a myriad of other risk factors can influence GA progression.[15] Lesion location affects progression, with extrafoveal lesions progressing faster than foveal lesions.[15-17] Lesion location was a key difference in the inclusion criteria between the two trial programs. Patients with extrafoveal lesions who receive avacincaptad pegol were determined to have a greater slowing of disease progression, versus patients in the pegcetacoplan trials that included both subfoveal and extrafoveal lesions. We must become better at identifying these baseline characteristics to decide which patients should be treated. In contrast to nAMD, it is not patient symptoms that will lead us to treat patients. It's incumbent on us to identify these characteristics and intervene earlier, where possible.

Dr. Orlin: The increased treatment effect over time with pegcetacoplan is reassuring. The pegcetacoplan trials looked at several functional outcomes. Visual acuity did not improve with time; however, post hoc microperimetry perilesional analysis in the OAKS trial showed a signal of functional preservation with pegcetacoplan.[12]

Dosing regimens were another important part of the trials. In nAMD, we use treat-and-extend (TAE) protocols in the real world. That is not being assessed with either drug. In the GATHER-2 trial, patients received monthly treatment over year 1, and then diverged into a monthly or every-other-month (EOM) regimen in year 2.[13] DERBY and OAKS evaluated monthly and EOM dosing schedules over the entire 2-year trial. We don't know how treatment intervals may change over time and how to decide if they could. The FDA label may eventually answer these questions, along with which patients might qualify for treatment and how to identify them.

Dr. Lalwani alluded to the fact that evaluating DERBY/OAKS and GATHER-2 is not an apples-to-apples comparison. A patient with subfoveal involvement could have been enrolled in DERBY and OAKS, but not GATHER-2. The conversation necessarily becomes very nuanced.

Dr. Gupta: These treatments would be a true paradigm shift in GA. For most treatments in retina, we've historically used functional or anatomic measures as retreatment criteria, to modify treatment regimens, and get patient buy-in. These GA drugs are potentially lifelong treatments to reduce progression, which equates to many injections. They will need strong patient buy-in. We're still grappling with questions of when to start treatment, how far from the fovea the atrophy needs to be to get the best outcomes, and how these things correlate with a patient's age and life expectancy.

Dr. Lalwani: Let's not forget that a sizeable portion of the treated eyes in both programs developed exudative AMD.[18,19] These patients were withdrawn from the phase 2 trials for both drugs, but the phase 3 trials continued to treat them with the assigned treatment and on-label anti-VEGF therapy. These data will be crucial going forward.

Dr. Wykoff: Across the two programs, the rates of new-onset exudative AMD were similar. Overall, history of fellow-eye nAMD and presence of nonexudative MNV in the study eye appeared to be risk factors for exudative AMD development in the study eye during the trial. More broadly, it's worth noting that about 15% of patients with intermediate AMD or GA may have nonexudative MNV.[20] We have developed a better appreciation of these lesions thanks to OCTA.[21-23] We also have a "double-layer sign" (DLS) on structural OCT, which corresponds to a shallow, irregular elevation of the RPE, and may be predictive of subclinical, nonexudative MNV in AMD.[24,25]

Q | Dr. Wykoff: Do any of you look for the nonexudative MNV lesions with DLS or OCTA?

Dr. Sridhar: Our understanding of what qualifies as pathologic nAMD has undergone a big shift during the past decade. There was a time when any neovascular complex or exudation was treated aggressively with anti-VEGF therapy. The CATT and IVAN trials then suggested that frequent anti-VEGF therapy could promote macular atrophy.[26,27] The jury is still out on this. Then, OCTA was used to show that patients can have nonpathologic MNV, which can remain quiescent for a long time. There's an interesting interplay between MNV and atrophy.

As Dr. Wykoff noted, several patients in the GA trials developed MNV, but what percentage were pathologic, and could some have been protective? Is the MNV part of how the drugs work? We don't know.

In my practice, I perform OCTA in patients who are at high risk for developing nAMD based on OCT characteristics. If I see a DLS or MNV without fluid, I take the conservative approach and don't treat them with anti-VEGF therapy. One reason is that I'm concerned of possible progression to atrophy. The other is that we now have better imaging to closely monitor these patients (every 3 to 6 months) and catch any exudation early. In my experience, many don't progress to nAMD.

Dr. Gupta: To Dr. Sridhar's point about the interplay between GA/dry AMD and nAMD—it's been suggested that complement pathway inhibition may induce a switch in macrophage polarization to promote a more proangiogenic phenotype, which could contribute to nAMD development.[28]

Dr. Sridhar: There exists a disconnect in what people flag as exudative AMD. We see that in DERBY and OAKS, for example. A greater proportion of these cases were flagged by the investigator versus confirmed by the reading center using fluorescein angiography.

All of this introduces more nuance into our treatment decisions.

"The risk of conversion to exudative AMD means we may need to inject and image every month. For that to be feasible, the OCTA acquisition time must become much faster."

—Jayanth Sridhar, MD

Whereas in the past we would've treated if wet and extended intervals if dry, now we'll have to consider if the patient is receiving GA treatment and if the MNV lesion is exudative. Again, the data pertaining to this subset of trial patients will be a good guide.

Dr. Wykoff: I previously noted that both trials had a similar rate of new-onset exudative AMD, but they were also limited in being able to consistently detect nonexudative lesions. Usually, this is done with OCTA and/or indocyanine green angiography, neither of which were performed routinely in either program. Even with OCTA, it can be hard to identify nonexudative MNV with minimal flow. We may need a combination of structural OCT and OCTA. In the context of these GA drugs, should we plan to adopt specific imaging protocols so that we are aware of nonexudative lesions before we start treatment?

Dr. Sridhar: Great point. Retina clinics are busy, so efficiency is key. The acquisition time for OCTA has improved, but it's not as fast as standard OCT. This risk of conversion to exudative AMD means we may need to inject and image every month. For that to be feasible, the OCTA acquisition time must become much faster. The second issue, at least in the United States, is reimbursement because we are not reimbursed separately for OCTA.

Q | Dr. Wykoff: We've discussed some of the trial data for both drugs. What do we consider the biggest data-gaps in our understanding of GA and these therapeutics?

Dr. Sridhar: Will these therapies help patients who don't currently have atrophy, but are at high risk of developing atrophy, ie, those with intermediate AMD? These patients were not included in the trials. Could we administer the treatment at an earlier stage of disease?

Dr. Gupta: We need guidance on the specific patient subpopulations who would benefit most from frequent, life-long injections.

Dr. Lalwani: As Dr. Orlin mentioned, the GATHER-2 trial is currently evaluating an arm in which the injection frequency is decreased in the second year. I'm hopeful these patients continue to have a reduced rate of progression, allowing us to tell patients that if they could commit to monthly injections in the first year, then the burden would be lessened in subsequent years.

Dr. Gupta: I'd like to see more robust functional data and, hopefully, tell patients that the drugs do eventually confer some visual benefit.

Dr. Orlin: I agree with Dr. Gupta. Unfortunately, because visual acuity loss can be slow with GA, significant changes may not be detected in relatively short-term trials. Therefore, benefits to visual acuity or other functional vision outcomes may require more time to become noticeable.

Dr. Sridhar: If we can buy patients more time with good vision, that's an immense benefit. It would also be interesting to subjectively assess whether we've been able to add to their quality of life. It's akin to cancer or dementia treatment outcomes, ie, extending quality of life over time. This might help guide which patients we choose.

Q | Dr. Wykoff: When you consider the data generated from both development programs, do any differences or similarities stand out to you?

Dr. Gupta: We've discussed many similarities: both drugs target the complement pathway, both reduce but don't halt progression, and both are associated with higher rates of new-onset MNV (of which a small proportion have been exudative).

Dr. Orlin: A key difference is the inclusion criteria of lesion location and the cohorts of patients who were enrolled as a result.

Dr. Wykoff: Let's discuss the concept of foveal involvement. Both programs have defined what this means for their particular programs, and it can be confusing. In the avacincaptad pegol trials, atrophic lesions could not involve the foveal center-point. If a lesion was even 1 µm from the center-point, so long as the fovea could be differentiated from the adjacent GA lesion by FAF, it was considered nonfovea-involving. Clinically and anatomically, we think of the fovea as a larger area, ie, the foveal dip, not necessarily just the center-point. One could argue that the avacincaptad pegol program did have a meaningful portion of patients who had foveal involvement, even if the center-point wasn't involved. This is semantics, but is that important?

Dr. Lalwani: When I think center-involving, I assume that visual acuity has been affected—directly tying anatomy with function. If therapeutics affect the subfoveal zone differently, then this area must be defined as specifically as possible in order to tailor treatment for patients with GA.

Dr. Wykoff: Nomenclature can be confusing. As a field, there is a need to standardize the definitions of these terms in the context of GA—foveal, subfoveal, extrafoveal—and what they mean in this

disease process. GA has two broad International Classification of Diseases (ICD)-10 codes: without subfoveal and with subfoveal. It will be interesting to see if this correlates with the FDA labels or if they will give a broader label to one or both drugs.

Q | Dr. Wykoff: Let's now focus on the safety profiles for both drugs. We live in a world that's very sensitive to intraocular inflammation (IOI), given some drugs have had real challenges with IOI. What do you think of the IOI data between the programs?

Dr. Sridhar: I'd like to know what criteria were used to define inflammation. Were they similar criteria across the programs? Was the inflammation clinically significant?

Dr. Wykoff: Great questions. In both trial programs, the investigators determined the presence or absence of inflammation and determined severity. So far, remarkably little inflammation has been reported with avacincaptad pegol. In comparison, 3.8%, 2.1%, and 0.2% of patients in the DERBY and OAKS trials developed IOI in the monthly, EOM, and sham arms, respectively, through 24 months.[12] Of these, 66% of were reported as mild, 14% were moderate, and 21% were severe.[12] Most of these patients who developed IOI continued treatment with pegcetacoplan without IOI recurrence, and there was no vasculitis or retinal involvement in any of these cases.

Dr. Lalwani: There were some reports of pegcetacoplan drug impurities in earlier formulations that resulted in severe IOI.[12,28,29] We need to know what percentage of patients with IOI had this exposure as well as their eventual long-term outcome.

TALKING TO PATIENTS ABOUT UPCOMING THERAPIES

Q | Dr. Wykoff: Let's assume pegcetacoplan and/or avacincaptad pegol receive FDA approval. How do you plan to communicate the efficacy profile for these drugs to patients?

Dr. Gupta: I'd reiterate what it means to have dry AMD and GA. I'd explain that they're losing vision in the areas affected by atrophy but retain central vision because atrophy hasn't reached that part of the retina yet. They may be experiencing no symptoms or have subtle impairment, like difficult reading in dim light; however, if these symptoms progress, they could begin losing central vision. I'd then introduce the drugs, communicating that they have been shown to slow atrophy, but not halt it. Hopefully, reduced progression will translate to delayed onset of significant vision loss.

Q | Dr. Wykoff: How would you communicate the safety profile?

Dr. Lalwani: These drugs are safe. The main possible side effect is the development of MNV, but we have effective therapies to treat this if it becomes an issue. Once vision is lost to GA, it is permanently lost. Even though the side effect profile is beneficial, is it acceptable for the monocular patient who has already lost vision in one eye to GA or nAMD?

"These drugs are safe. The main possible side effect is the development of MNV, but we have effective therapies to to treat this if it becomes an issue. Once vision is lost to GA, it is permanently lost."

–Geeta Lalwani, MD

Dr. Gupta: Compliance is another consideration. If patients are started on these GA treatments and can no longer be compliant for whatever reasons, that's less of an issue than if the treatments contributed to conversion to exudative AMD, which is inadequately treated due to compliance issues.

Dr. Sridhar: We do a risk assessment with every new drug, considering if the patient has other options, the threat of vision loss, and the safety issues highlighted in the clinical trials. The trials cannot capture every conceivable safety issue. Most of us are conservative with new drugs, and this is a slower progressing disease compared to nAMD. That will influence the adoption rate for specific patient subpopulations.

A monocular patient who has lost vision in one eye to GA and is teetering on the edge of foveal involvement in the other eye may not be the first patient I treat with the drug. It may be the patient with bilateral GA who is very motivated to begin therapy. Even with this patient, I wouldn't begin with bilateral therapy.

Dr. Wykoff: Which patients will you first discuss these therapies with? Are there any with whom you won't discuss these therapies?

Dr. Sridhar: I'm already discussing these therapies with a lot of patients. It's worth mentioning them to patients with intermediate AMD or even early AMD, especially if they have a family history of AMD.

I wouldn't mention these therapies to patients who have advanced bilateral GA, ie, 20/400 VA or count fingers in both eyes. The VA cutoffs in the trials were 20/320.[12,13] There wouldn't be much clinical relevance in having that conversation.

Dr. Wykoff: Having nAMD in the study eye was exclusionary to enrollment in these trials. As we have discussed, some patients developed new-onset exudative AMD during the trials. These patients were treated concurrently during the trials, so we do have some data indicating that concurrent treatment with anti-VEGF therapy and either of these drugs can be well tolerated. The cohort of patients in our clinic today with nAMD and concurrent GA, represent a very large population of patients who may benefit from these therapies. Many patients

who are currently on anti-VEGF therapy for nAMD note progressive vision loss due to progressive atrophy.

Q | Dr. Wykoff: How do you plan to incorporate GA therapies into your current treatment algorithm for patients with nAMD who are receiving anti-VEGF therapy?

Dr. Lalwani: The SEVEN-UP trial, which observed patients with nAMD from the pivotal ANCHOR and MARINA trials as well as the open-label extension HORIZON trial, showed a mean loss of 8.6 letters from baseline, even while patients remained on ranibizumab injections.[30] This is perhaps the largest subpopulation who may need treatment.

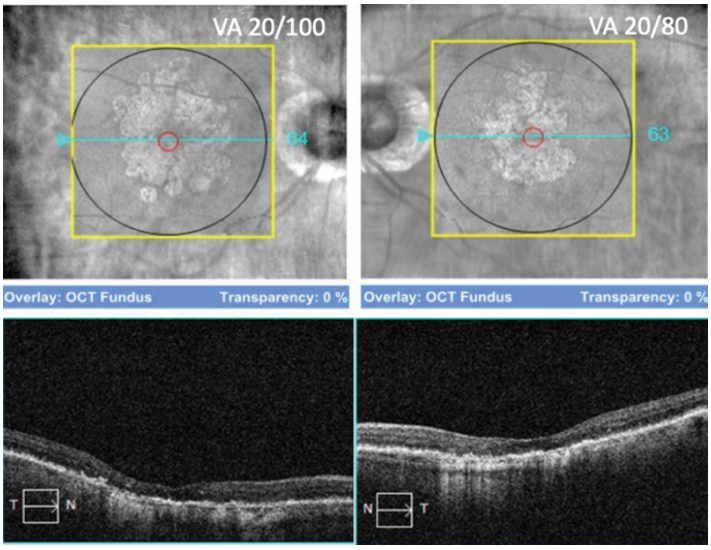
Dr. Wykoff: I agree. Anecdotally, macular atrophy secondary to nAMD can remain static for years in some patients and demonstrate more typical atrophic progression in others. Ideally, we'd be able to differentiate between eyes with stable areas of atrophy and those with progressive atrophy that may benefit from anticomplement therapies.

Dr. Orlin: Because these trials didn't specifically include these patients, it's unclear how applicable the data will be to this subpopulation. We also don't know whether they are experiencing the same disease process as those with primary GA, and if and how that might affect treatment efficacy. How were the patients who developed new-onset exudative AMD treated in the GA trials?

Dr. Wykoff: In both programs, the anti-VEGF agent and investigative product were administered on the same day with approximately 30 minutes between injections. We waited until IOP was normalized after the first injection and then administered the second injection.

We've done multiple injections in trials for a long time, but this approach did raise some safety and efficacy questions that remain incompletely answered. The trial data suggest that these patients performed as well as the broader population, in both regards. However, this was a relatively small cohort. The trials were not structured to measure differences between this population and the broader population.

Dr. Sridhar: Retina clinics are extremely busy with patients who need therapy for immediately vision-threatening diseases. Sometimes we spend weeks tailoring treatment regimens to optimize efficacy. How do we now fit in GA treatments? Initially we'll treat patients monthly or EOM; TAE regimens won't be studied and validated for several years. How do we restructure clinic flow? Dr. Lalwani mentioned partnering with other allied health professionals and the concept of asynchronous screening with testing, followed by treatment. At-home monitoring or testing will further speed up the process. However, there's only so many injections that we can feasibly fit into a day. We've talked about slow adoption in the beginning, but if these treatments work, what will we do in 2 to 5 years when they're better established?



Courtesy of Mrinali Gupta, MD

Figure 1. An 80-year-old woman with bilateral fovea-involving lesions who has had vision loss for years.

Dr. Gupta: The push for longer-acting nAMD treatments becomes even more urgent.

CASE 1: THE IDEAL CANDIDATE?

Dr. Gupta: This is an 80-year-old woman who's had vision loss for years. She has 20/100 VA in the right eye and 20/80 VA in the left eye, with bilateral fovea-involving GA (Figure 1). Her lesions are irregularly shaped and both eyes show high-risk features on FAF (not shown). She still has relatively good vision and seems like an ideal early candidate to try these treatments.

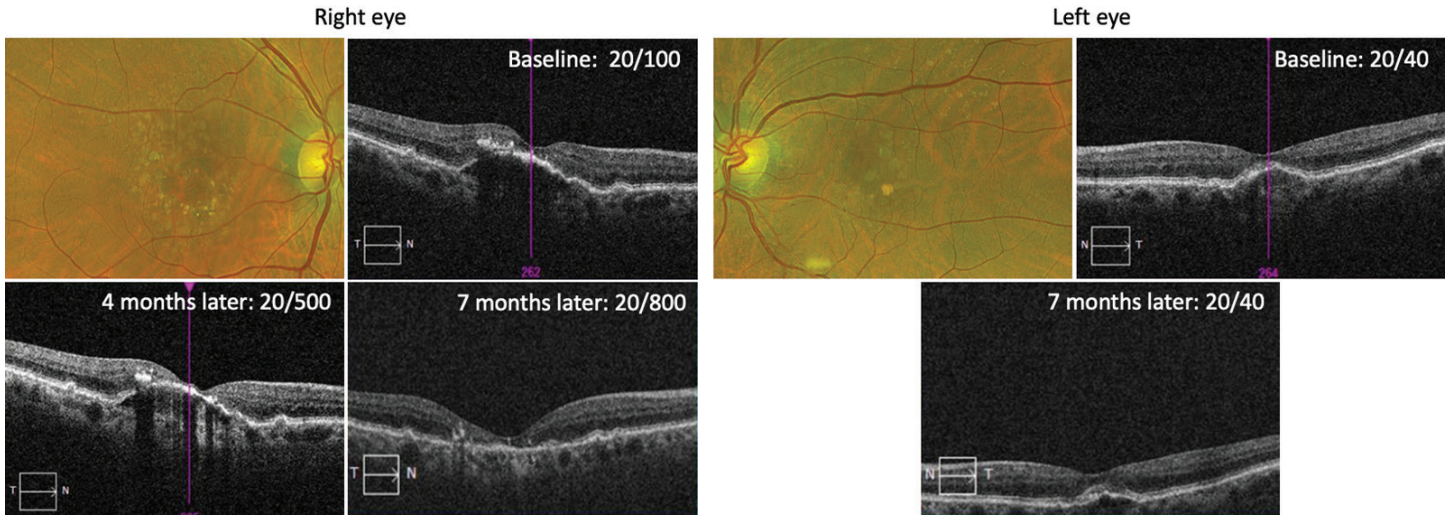
Dr. Sridhar: I would do the grandma test—would I treat if this were my own grandmother? My answer would be yes, based on the current trial results. On subgroup analysis, some patients with visual acuity in this range did have significant worsening despite therapy, so there would be some concern that treatment may not matter. Still, if she's motivated, I'd go for it.

Dr. Gupta: Yes, her vision is midrange in the context of the visual acuity included in the trials.

Dr. Orlin: I agree with Dr. Gupta. This patient would be motivated to maintain her vision instead of having it progress.

CASE 2: PED COLLAPSE LEADING TO ATROPHY

Dr. Gupta: This is an 80-year-old patient whose right eye had 20/100 VA, with a large pigment epithelial detachment (PED) at baseline (Figure 2). At this time, OCTA and fluorescein angiography showed no MNV under the PED. The left eye also had a regular PED at baseline but showed no signs of MNV. The right eye progressed within 7 months to photoreceptor and outer retina atrophy over the collapsed PED. Eventually, the left eye also showed some abnormalities overlying the PED, leading to some concern that this eye may also develop atrophy.



Courtesy of Mrinali Gupta, MD

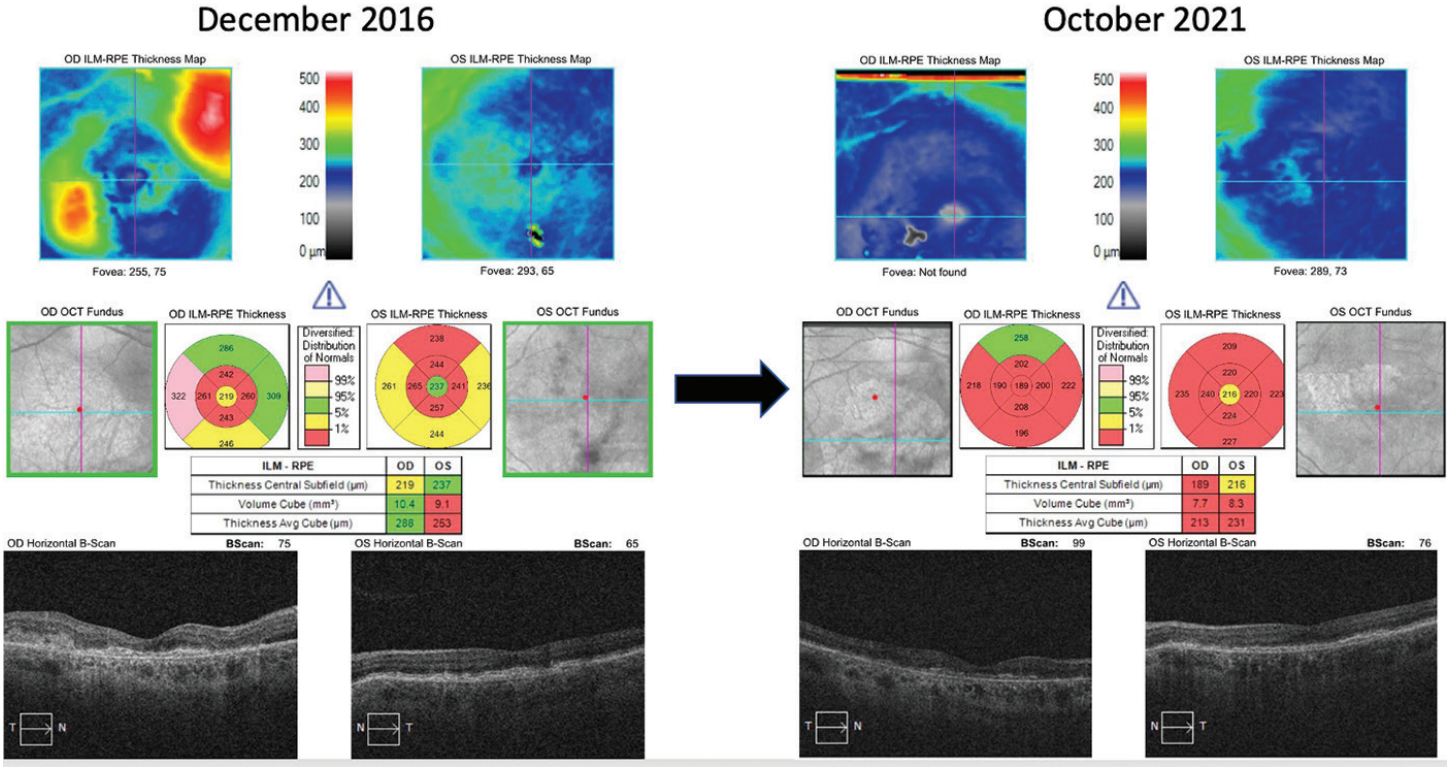
Figure 2. An 80-year-old woman with PED in right eye progressing to atrophy.

Dr. Lalwani: Ideally, these patients should receive early intervention because the progression to atrophy upon PED collapse is so rapid. However, a prospective study is needed to gauge whether these eyes would be equally good candidates for GA treatments.

Dr. Wykoff: Great case. We seem to discuss PEDs in the context of nAMD more frequently than dry AMD. This case was identified at baseline as having dry AMD. Some may have administered anti-VEGF injections and then termed the ensuing atrophy as anti-VEGF-associated, but we see that the atrophy progressed even without the injections. This highlights how difficult it can be to discern between atrophy arising from anti-VEGF treatment compared to the natural progression of AMD. The patient already had relatively limited vision at baseline, but the rapid anatomic progression of atrophy resulted in more substantial vision loss.

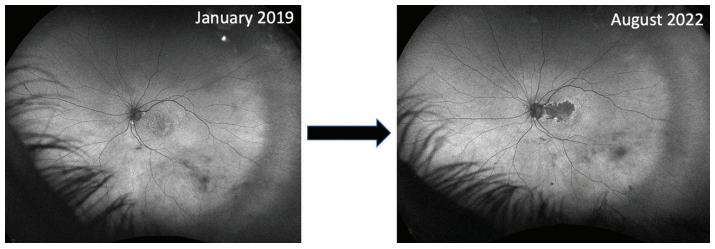
CASE 3: THE MONOCULAR PATIENT

Dr. Lalwani: This patient developed nAMD in the right eye



Courtesy of Geeta Lalwani, MD

Figure 3. Patient with extensive GA in the right eye in December 2016 following a previous nAMD diagnosis. By October 2021, a DLS was obvious on the OCT image of the left eye, denoting the presence of type 1 MNV.



Courtesy of Geeta Lalwani, MD

Figure 4. Progression of extrafoveal atrophy in the left eye of a patient with GA in the right eye.

almost a decade ago, which was soon followed by rapid onset of extensive GA (Figure 3). Her left eye has been stable with 20/20 VA. In early 2021, her left eye developed a peripapillary hemorrhage, which we initially decided not to treat until it progressed to subfoveal fluid. We treated her left eye with intravitreal bevacizumab until the fluid fully resolved, and then continued to monitor her eye. In October 2021, the OCT of her left eye demonstrated a DLS, indicating the presence of type 1 MNV (Figure 3). Additionally, you can see the progression of extrafoveal GA over the years (Figure 4), even though she has maintained good visual acuity in this eye.

In theory, we might want to start using GA therapies on patients who have lost some VA, ie, 20/80 or 20/100, but should we think twice before treating patients with a history of nAMD, or subclinical type I MNV?

Dr. Orlin: We need more data from the trials, on the patients who developed exudative AMD during GA treatment and vice versa. We'll need to carefully monitor for nAMD conversion and treat when this occurs. For now, I'm not sure I'd treat GA secondary to nAMD until we have more data, particularly if the patient is undergoing continued anti-VEGF therapy.

Dr. Wykoff: I agree with Dr. Lalwani. This is a great patient to treat. We can watch for rebleeds very carefully and control them.

CASE 4: BILATERAL GA—WHICH EYE WOULD YOU TREAT?

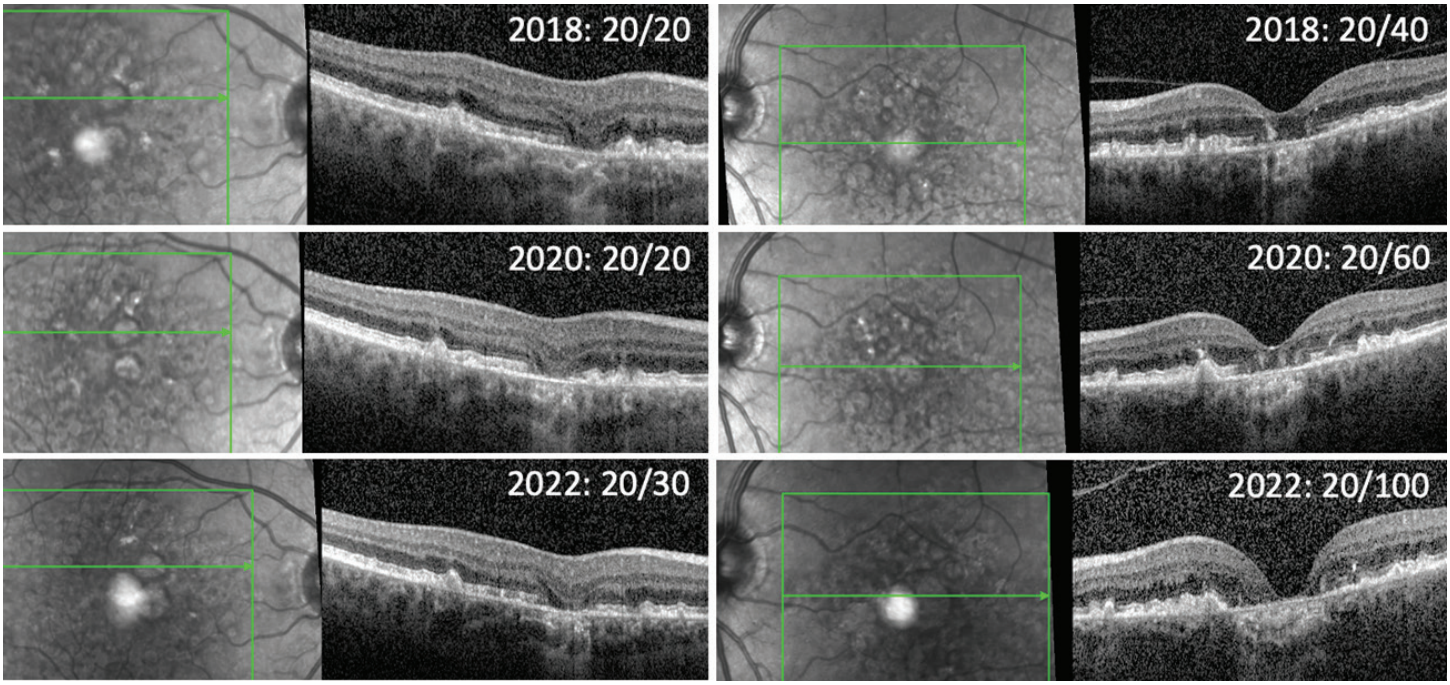
Dr. Orlin: This is a 68-year-old man with bilateral GA. In 2018, the right eye had parafoveal GA with 20/20 VA and the left eye had subfoveal GA with 20/40 VA (Figure 5). In 2020, the right eye was stable at 20/20 VA, but the left eye showed progression and VA dropped to 20/60. The most recent exam in 2022 shows the left eye has progressed to 20/100 VA with eccentric vision.

Dr. Wykoff: Great example of an atrophic lesion in the right eye that didn't progress over time, and one in the left that did progress substantially.

Dr. Orlin: Fortunately, he's still seeing well out of the right eye, but it may also eventually progress with time.

Dr. Lalwani: Did the GA studies evaluate whether the drugs reduced the expansion of existing lesions or decreased the presentation of new lesions?

Dr. Wykoff: Both clinical programs showed there was reduced conversion of iRORA to cRORA,[31,32] and the drugs appeared to decrease the development of new areas of GA and slow expansion of existing lesions. Following this line of thought, could these



Courtesy of Anton Orlin, MD

Figure 5. A 68-year-old man with varying rates of GA progression in both eyes.

drugs be used to prevent the development of GA in eyes with intermediate AMD and high-risk features? This is an important clinical question that both companies have discussed analyzing through clinical trials but have been hesitant to initiate due to uncertainty regarding the appropriate primary endpoint.

Dr. Orlin: I'm seeing this patient again in 4 to 6 months. If the drugs are approved by then, I'll use OCT scans to discuss his options. He may be motivated to have the left eye treated to preserve vision, and the right eye treated given the vision he has already lost in the left.

Dr. Wykoff: As you note, without counseling, this patient may initially want to treat the eye that's lost vision. It's analogous to patients with proliferative diabetic retinopathy who have a tractional retinal detachment (TRD) with vision loss in one eye and flat areas of neovascularization but good central vision in the other. These patients are often focused on the eye with vision loss and the TRD, while the clinician may be particularly focused on the fellow eye in hopes of preventing vision loss in that eye. How would you have that conversation?

Dr. Orlin: I'd temper expectations and clearly state that these treatments will not return lost vision. The right eye still has good vision, so we want to prevent atrophy in that eye from progressing as it did in the left.

Dr. Wykoff: That's a great concept—using the fellow eye as a guide for the potential rate of progression in the better-seeing eye.[15]

Dr. Sridhar: I'd begin with treating the worse-seeing eye for the first month or two, to observe safety, with the ultimate goal of bilateral treatment. Starting with the left eye may seem counterintuitive, but we don't know if this eye will still be the worse-seeing eye in 5 to 10 years. It may be that 20/100 VA in the left eye will be the best visual acuity that the patient retains. As long as neither eye is end-stage, I would try to preserve as much vision as possible.

Dr. Wykoff: We briefly discussed that end-stage eyes were not included in the trials. Some of those patients remain very anxious about progression and state that their vision is progressively deteriorating. Many of these patients are asking for some treatment. Using the clinical tools available today, most of these patients have already lost most of their quantifiable visual function and so it's challenging to know how to approach these situations. Would you consider treating such patients?

Dr. Sridhar: I think of patients with disciform scars who have count fingers vision and nAMD. We don't treat most of these patients. Occasionally, some eyes will continue to bleed and exude at the lesion edges. If patients have bilateral scars and exudation, they may notice their visual fields becoming affected. I think it's reasonable to treat those patients, but we know there won't be any dramatic changes in vision. The challenge is to manage expectations.

Dr. Lalwani: I'd find it hard to justify treatment given the treatment burden of these GA drugs and the fact that we're only slowing progression. If the eye was to develop endophthalmitis, that could significantly affect the patient's existing vision.

CASE 5: WHICH EYE WILL FARE BETTER IN THE LONG-TERM?

Dr. Sridhar: This patient came to me for a second opinion 3.5 years ago. He was diagnosed with advanced dry AMD in the right eye and nAMD in the left eye. VA was 20/200 in the right eye and 20/25 in the left eye. He was receiving monthly aflibercept injections with an outside provider and was terrified of losing vision. The OCT showed the eye was dry, so we talked about extending his intervals or injecting as needed, but he was adamant about keeping up with monthly injections with his physicians for fear of losing his sight. During the next few years, he continued monthly injections outside of our practice but returned every 6 to 12 months for a second opinion.

From 2019 to 2020, VA in the left eye dropped from 20/20 to 20/30, and we can see atrophy developing (Figure 6). The next year he reported that he'd lost the ability to read, and VA became 20/100. During the most recent visit, the left eye had progressed significantly to 20/400 VA. Ironically, his right eye at 20/200 VA is the better-seeing and dominant eye.

This case makes me question whether this was anti-VEGF-mediated macular atrophy or natural history of disease. The progression over 4 years is so dramatic that it could've been the former. To be fair, the right eye never received anti-VEGF injections and we don't know how quickly that progressed.

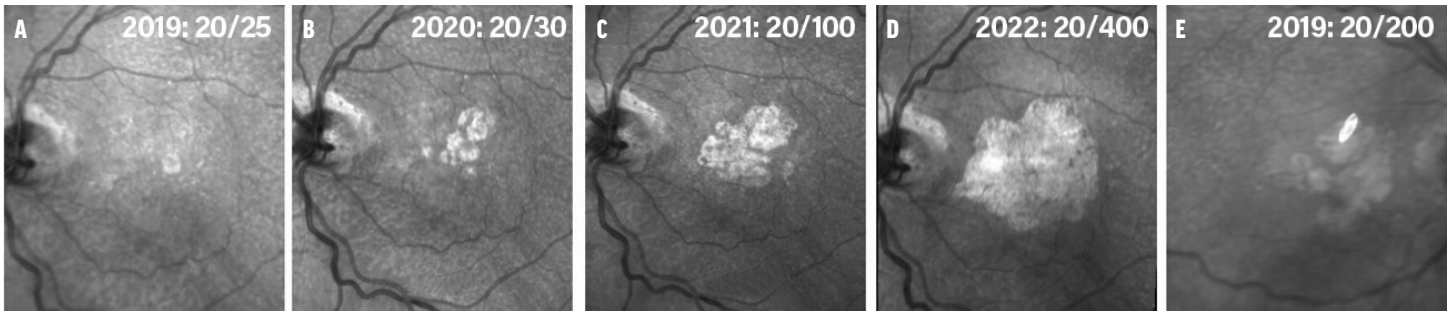
If we can't predict which eye will fare better or worse in bilateral advanced AMD, how aggressive should we plan to be when treating atrophy? How should we balance anti-VEGF therapy and complement inhibition?

Dr. Wykoff: There is literature to support both sides of this debate but, on average, my interpretation of the literature is that anti-VEGF therapy does not cause significant macular atrophy progression.

Dr. Lalwani: It depends on the motivation of the patient. This case demonstrates a situation of treating the patient rather than the signs. Clearly, this was a very motivated patient.

Dr. Wykoff: Do we think that GA treatment could similarly become more patient-driven? For example, end-stage patients may choose to undergo treatment despite our counseling. When they realize that their vision is not improving, they may forego continued treatment.

Dr. Lalwani: Possibly, in very specific cases. More often, for patients with extrafoveal GA lesions or those with high-risk features in intermediate AMD, retina specialists will be the driving



Courtesy of Jayanth Sridhar, MD

Figure 6. Patient with nAMD in the left eye (A-D) and advanced dry AMD in the right eye (E), who developed macular atrophy in the left eye after 4 years of monthly anti-VEGF injections.

force behind treatment initiation, counseling patients on their risk of progression. In 10 years, we may have a better idea of the ideal patient profile for treatment and, as Dr. Sridhar noted, have algorithms that generate atrophy progression scenarios with and without treatment. That is what we need to show patients.

Dr. Sridhar: I completely agree with you. We know that we undertreat patients with nAMD in the real world. Some of that is poor patient compliance but most of it is physician-driven.[33] Whether the difference is clinically meaningful can be debated. With GA, we'll now have a disease where there is little guidance on who to treat, how to treat, whether treatment can be extended, or even a quick standard to gauge treatment response.

Physician education is going to be very important. There will be slow adoption among retina specialists, initially, but this could pick up. The inflection point may be 6 to 18 months into treatment, when fatigue sets in on the clinician's end. They may understand the trial data well, but if they don't see any changes in their patients, they may lapse on strict monthly injections. We still don't know whether treatments will be as effective if the intervals are widened. Therefore, physician education is going to be a huge part of ensuring success. Patients will only be as motivated as their doctors. ■

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GEOGRAPHIC ATROPHY MANAGEMENT: THE ROLE OF COMPLEMENT MODULATION-BASED THERAPIES

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Expiration Date: April 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, please go to https://evolvemeded.com/course/2250-supp. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

Please type or print clearly, or we will be unable to issue your certificate.

Name _____ DOB (MM/DD) _____

Phone (required) _____ Email (required)* _____

Address/P.O. Box _____

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**Evolve does not share email addresses with third parties.*

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
Review updates in the classification for dry age-related macular degeneration, in particular the significance of incomplete retinal pigment epithelial and outer retinal atrophy (iRORA) and complete retinal pigment epithelial and outer retinal atrophy (cRORA)	_____	_____	_____
Appraise anatomical retinal features that may serve as biomarkers of geographic atrophy (GA) progression	_____	_____	_____
Identify lesion-specific factors that may predict treatment response	_____	_____	_____
Describe the role of the complement pathway in GA development and progression	_____	_____	_____
Critique clinical trial evidence for pipeline complement modulation-based therapies	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to manage patients with 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. Which of the following OCT features may serve as a biomarker that portends a higher risk of progression to GA?

a. Hyporeflective foci overlying drusen
b. Hyperreflective foci within drusen
c. Reticular pseudodrusen
d. Absence of drusen

3. All of the following represent good ways to determine functional vision in patients with age-related macular degeneration (AMD), EXCEPT:

a. Contrast sensitivity
b. Reading speed
c. Low luminance visual acuity
d. Snellen visual acuity

4. You are seeing a 78-year-old man with nonneovascular AMD. His GA has been progressing, and he is increasingly disturbed by his visual function. He is eager to seek therapy for his GA, but wonders about potential side effects. Which of the following statements about GA therapeutic side effects is true?

a. There is a significant risk of intraocular inflammation with GA therapies
b. There is a risk of the development of macular neovascularization with GA therapies
c. There is a high risk of endophthalmitis with GA therapies
d. There is a high risk of angle-closure glaucoma with GA therapies

5. An 80-year-old woman presents to your office for evaluation. Her BCVA is 20/100 OD and 20/80 OS. She has bilateral fovea-involving GA. Her fundus autofluorescence photos show a pattern of GA that is considered high risk in both eyes. Which of the following statements is the most reasonable option for this patient?

a. Do not consider GA therapy for this patient because her disease is bilateral and high risk
b. Do not consider GA therapy for this patient because her GA is fovea-involving
c. Consider GA therapy for this patient because her vision is midrange and in the context of the visual acuity included in GA therapy trials
d. Consider GA therapy for this patient but only in her left eye

6. An 80-year-old man with AMD presents to your office for evaluation. His OCT demonstrates a zone of retinal pigment epithelium (RPE) attenuation and choroidal hypertransmission 300 µm with overlying photoreceptor degeneration. Which of the following statements is true about this patient?

a. This patient has OCT evidence of incomplete RPE and outer retinal atrophy (iRORA) and has high risk of GA progression
b. This patient has OCT evidence of complete RPE and outer retinal atrophy (cRORA) and low risk of GA progression
c. This patient has OCT evidence of iRORA and low risk of GA progression
d. This patient has OCT evidence of cRORA and high risk of GA progression

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 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:

_____

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

_____

_____