UNTIL RECENTLY, CLINICIANS HAVEN’T had a viable option to treat geographic atrophy (GA). This absence of treatment has presented a considerable gap in patient care, considering that the disease poses a significant risk of blindness.

Now, two new therapeutics appear to show success in slowing the growth rate of GA lesions. These treatment advances are based on evidence that genetic changes associated with the complement genes and the complement cascade play a role in age-related macular degeneration (AMD). Other advances in the GA field include high-resolution OCT imaging and deep-learning algorithms that have revealed subtle biomarkers, which have helped fine-tune the diagnostic criteria for GA and define the targets for new therapies.

New Terminology, New Role for OCT
“The field is moving toward a new definition of GA that employs OCT,” said Eleonora Lad, MD, PhD, at Duke University Medical Center in Durham, North Carolina. While fundus autofluorescence (FAF) and color fundus imaging have been the gold standard for diagnosing GA, “we feel that OCT is best because it allows 3D and high-resolution visualization to diagnose atrophy more accurately,” she said.

Recently, the Classification of Atrophy Meetings (CAM) group, a collaboration among international experts in retinal imaging, published two reports: one suggested new terminology based on OCT findings,1 while the other validated these terms as biomarkers for future research.2

New terms: iRORA and cRORA. These new terms refer to early features of retinal cell death based on the anatomic layers affected, including the retinal pigment epithelium (RPE). iRORA, for Incomplete RPE and Outer Retinal Atrophy, refers to pre-GA lesions, while cRORA refers to Complete RPE and Outer Retinal Atrophy. The CAM group noted that the term “nascent GA” should be used for “a subset of AMD-associated iRORA in the absence of past or current neovascularization to signify that the progression toward GA has begun.”

The CAM group defines cRORA as having an area of choroidal hypertransmission of 250 µm or more in diameter, an area of disrupted or attenuated RPE of 250 µm or more in diameter, and overlying photoreceptor degeneration without an RPE tear. In turn, iRORA is defined as including these OCT signs but with smaller lesions.

Why OCT is key. The OCT imaging modality drives the diagnosis of cRORA and iRORA. “GA is a color-imaging diagnosis, while cRORA is diagnosed based on OCT, which is far more sensitive,” said Philip J. Rosenfeld, MD, PhD, at the Bascom Palmer Eye Institute in Miami.

“Both cRORA and iRORA are defined using horizontal OCT B-scans, which show loss of the outer retina and RPE, as well as the presence of hypertransmission defects, which means light is getting into the choroid that would normally be blocked by the RPE,” Dr. Rosenfeld said. In addition to using single B-scans as recommended by the CAM group, “another strategy is to use a
In Search of Better Biomarkers
Beyond BCVA. “The new paradigm is to recognize that BCVA is not a good biomarker for GA trials,” said James T. Handa, MD, at the Wilmer Eye Institute in Baltimore. “Functional endpoints will be invaluable for future clinical trials to assess treatment validity, but the field hasn’t identified them.” Researchers are diving deep into OCT analyses for subtle changes that reflect disease activity, Dr. Handa said. “There’s evidence, for example, that the ellipsoid zone [EZ] line becomes less visible, suggesting loss of mitochondria in the photoreceptors, and mitochondrial dysfunction is a known pathogenic factor in AMD,” he said. “So if you could integrate functional assays with structural changes, you’d have more robust findings than structural or functional assays alone in clinical trials.”

Since dim-light vision is challenging for intermediate AMD patients, one promising functional endpoint is a low-luminance VA test, said Dr. Handa. Functional endpoints could be developed from other tests, including microperimetry testing for visual deficits, mesopic microperimetry to measure low-light vision loss, delayed dark adaptation, and contrast sensitivity testing, he added.

In addition, Dr. Lad pointed out, “New artificial intelligence [AI] algorithms can analyze multimodal imaging of all kinds to help correlate structure with function, which will become increasingly important for GA management.” For instance, in a recent post hoc analysis of data from the phase 2 FILLY trial, researchers conducted an AI-based morphologic analysis of the efficacy of pegcetacoplan (Apellis) in treating GA.

Key biomarker: choroidal hypertransmission. Choroidal hypertransmission is one of the more robust, consistent biomarkers for GA, said Dr. Rosenfeld.

When atrophy is viewed using an en face strategy, “a bright spot measuring 250 µm in any dimension is referred to as persistent hyper-transmission defect, and this has been shown to progress to typical GA,” said Dr. Rosenfeld. “The advantage of en face imaging is that these hyper-transmission defects can be seen in any en face dimension, and their growth can be measured just as we measure atrophy growth using FAF imaging.”

It’s a structural defect that’s easy to grade, he said, adding, “Graders from Bascom Palmer and the CAM group showed 97% agreement and an overall positive predictive power of 99% in detecting these defects.” OCT modalities, such as OCT angiography (OCTA) and swept-source OCT (SS-OCT), can detect the earliest changes that lead to typical atrophy and identify which layers of tissue are damaged. “We can measure photoreceptor integrity around the atrophy, blood-flow deficits in the choriocapillaris within the macula, and basal laminar deposits [a type of drusen] around the atrophy,” said Dr. Rosenfeld. “All of these measurements help predict the growth rate of atrophy and can be obtained from a single OCT scan.”

Additional biomarkers. Other biomarkers associated with GA progression from earlier studies include lesion area, number, shape, location, and direction of growth relative to the fovea.

Novel Therapies: Complement Inhibitors
Two new drugs target the complement system. If FDA-approved, both would require monthly intravitreal injections.

“There are at-risk genes that are clearly causative or demonstrate an at-risk phenotype for AMD,” said Dr. Rosenfeld. “The good news with these drugs is that we can slow down disease progression; the bad news is that we can’t recover lost vision because the atrophy can’t be repaired.”

Pegcetacoplan. Pegcetacoplan inhibits comple-
ment component 3 (C3). In the phase 3 OAKS trial, researchers compared monthly and bimonthly pegcetacoplan with sham intravitreal injections at 12, 18, and 24 months.

The 12-month Apellis data are under review, said Dr. Lad, the OAKS trial’s international principal investigator. “OAKS is the first large phase 3 trial in GA that met its primary endpoint,” she said. “In the parallel phase 3 DERBY trial, pegcetacoplan reduced GA lesion growth versus sham, but statistical significance wasn’t reached, though data from both studies were submitted to the FDA.”

Both OAKS and DERBY used the same structural endpoint as the FILLY trial did: change in size of lesions from baseline. In FILLY, pegcetacoplan had a 29% and 20% reduction, as measured by FAF, after monthly and every-other-month [EOM] injections, respectively. According to two-year data from Apellis, the OAKS investigators saw a reduction in lesion growth of 22% with monthly injections and 18% with EOM injections compared to sham. Results of DERBY showed a slightly lower effect: 19% with monthly injections and 16% with EOM.

“Two-year data are positive,” said Dr. Rosenfeld. “We can slow the progression of GA using this C3 inhibitor.” But the results have yet to be peer-reviewed. “The devil is in the details, so it’s hard to know more than what the [company’s] press release states,” said Dr. Handa. The drug seems to need 18 or 24 months to show results, Dr. Handa added. “You’re asking patients to invest far into the future, but it’s the best we have, so we’ll probably use it in selected cases if approved.”

Avacincaptad. Avacincaptad pegol (Iveric Bio) inhibits complement component 5 (C5). The drug was evaluated in two phase 3 studies, GATHER1 and GATHER2, both of which used the structural endpoint of growth rate in lesion size, measured by FAF at baseline, month 6, and month 12. According to the company, the mean rate of growth in GA area from baseline to month 12 was 35% for the 286 participants in GATHER1 and 18% for the 448 participants in GATHER2.

“With GATHER2, the original trial design was quite savvy,” Dr. Handa said. “Different-sized lesions grow at different rates, and the study randomized control and treatment groups with similar lesion features to compare apples to apples, which could make a substantive difference in recognizing a defined change after treatment.”

Cautious optimism. “We may identify subtle differences between effectiveness and safety profiles of these two complement inhibitors as we gain more information from the clinical trials,” Dr. Rosenfeld said.

Pathogenesis: HTRA1 Offers a Case in Contradiction

To illustrate the mysteries of the pathogenesis of GA, consider the role of the HTRA1 gene.

Genentech developed an intravitreal anti-HTRA1 therapy with the goal of reducing GA enlargement, said Dr. Handa. “Later, a very high-profile lab published a paper showing that the HTRA1 gene regulates the extracellular matrix and keeps the RPE and outer retinal-brain barrier healthy,” he said. “So one study concluded that embellishing HTRA1 would be a potential treatment for AMD, whereas the clinical trial was inhibiting HTRA1.”

These contradictory findings underscore the need for collaborative research to prioritize the mechanisms of disease so new therapeutics are developed in a cost-effective manner, Dr. Handa said. Moreover, following the European Union’s approach to investing in collaborative research that tests competing theories on AMD would be a way forward, he added.

Of note, however, complement inhibitors only slow, but do not stop, the progression of disease. “These drugs bend the curve of progression, and the hope is that over time the rate of progression slows and plateaus,” said Dr. Rosenfeld. “The vast majority of my patients are excited because [these drugs present] an option not available before.”

**What about risk of exudation?** Both of these complement inhibitors can trigger exudation—a further complexity in treating the dry form of advanced AMD. “Using SS-OCTA, we’ve identified abnormal vessels under the RPE long before exudation developed,” said Dr. Rosenfeld. “The blood vessels start growing but aren’t leaking, and we believe that growth is a good thing: those vessels are bringing the blood supply closer to the RPE and outer retina because the choriocapillaris has been damaged.”

Does this represent a paradoxically healthy “bypass” mechanism? “It’s the body’s attempt to resupply the outer retina and RPE with nutritional and blood supply,” he said. “It’s only when those vessels start leaking that we run into problems.”

Dr. Rosenfeld pointed out, “Everyone with AMD starts with dry macular degeneration, and why some eyes progress to wet is a mystery. With anti-VEGF therapy, we can convert wet AMD back to dry, but if patients live long enough, they’ll eventually lose vision from the progression of the dry AMD. With these new complement inhibitors, we’ll have a treatment for GA, and if we treat early enough, we’ll be able to preserve as much vision as possible.” He added, “Exudation doesn’t scare us anymore. Atrophy scares us.”

“Patients need to be counseled that if they convert to wet AMD, they’ll need two injections, one for wet, one for dry,” Dr. Lad noted. “That’s been well tolerated in studies, and my patients would accept this possibility because GA is such a debilitating disease.”

**Going Forward: Continuing Challenges**

**In pursuit of earlier intervention.** The holy grail in GA is earlier intervention. “The greatest challenge retina specialists face right now is to treat at the intermediate stage to preserve vision and prevent the atrophy from forming,” said Dr. Rosenfeld.

“Intermediate macular degeneration is characterized by drusen, which are focal elevations of the RPE full of lipid and protein, but these patients often have good vision in normal lighting.”

Enter AI. Early diagnosis remains a priority,

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**Dietary Impact on GA Development and Progression**

There’s new evidence that diet can help patients at risk for GA. Using data from the Age-Related Eye Disease Study 2 (AREDS2), NEI researchers found that a “Mediterranean-style” diet was associated with both a delay in progressing to GA and a slower growth of lesions themselves.1

“It’s an observational study, but the effect size is pretty amazing,” said Emily Y. Chew, MD, at the NEI. “The reduction in growth rate of the GA lesion is significant, when comparing those with high adherence to the Mediterranean-style diet to those with low adherence.”

**Risk reduction.** Those with greater adherence to the diet experienced “about a 30% reduction in the risk of developing GA,” Dr. Chew said. And in the subset of participants without large drusen, she added, “there was a 20% reduction in developing large drusen.”

Thus, she said, “It seems that diet has an effect early on, and even if a patient already has intermediate AMD, it’s never too late, and you can still reduce the rate of having late AMD.”

When individual dietary components were assessed, the results showed that the single most important factor related to a lower risk of developing GA is a higher intake of fish, said Dr. Chew. The four factors related to delaying GA enlargement were a higher intake of whole fruits, less red meat, moderate alcohol, and a better ratio of monounsaturated to saturated fatty acids, she added. Her take on these findings: “We need to eat a healthy diet, period.”

Dr. Chew noted the underlying genetic complexities inherent in AMD, saying that genes can be either problematic or protective, thus adding to or subtracting from the diet’s effect. For example, she said, “If you have a protective gene for complement factor H and you also eat fish, it markedly reduces the risk of progressing to late AMD, particularly for GA.”

**Glycemic index.** In other dietary news, “There’s also strong preclinical laboratory research2 to support a low–glycemic-index diet,” Dr. Handa noted. “If sugar gets into the bloodstream too quickly, it causes structural changes to proteins and lipids that cause damage and contribute to AMD; epidemiologic data show that.”

1 Agrón E et al. Ophthalmol Retina. 2022;6(9):762-770.
although the absence of symptoms in the intermediate stage makes this difficult. Toward that end, the Collaborative Community on Ophthalmic Imaging, a consortium that includes NEI, FDA, and academic groups, is developing AI methodologies for earlier diagnosis of patients with AMD.

“There’s been an explosion of new AI methods for AMD screening and for prediction of conversion from intermediate to advanced stages,” said Dr. Lad. Using a machine-learning analysis on a large dataset of intermediate AMD images, for instance, her group was able to “stratify patients into four risk levels, telling us which patients are more likely to progress to GA,” she said. That work used biomarkers of disease progression in intermediate AMD based on spectral-domain OCT.

Machine learning requires access to expert human graders of OCT, she added. “The next step will be deep-learning algorithms that use retinal images alone to predict progression. At Duke we have developed and are validating an AI algorithm based on OCT alone, without needing costly and time-consuming human gradings, that predicts progression from intermediate AMD to GA.”

Still unknown: pathogenic pathways. Multiple pathogenic pathways have been proposed for GA, said Dr. Handa, whose research focuses on molecular mechanisms of normal aging versus those seen in early AMD. “We don’t have a prioritized rank of what’s causing disease,” he said. “Is it complement? Is it oxidative stress? Is it mitochondrial dysfunction? We don’t know which is most important.

“We also don’t know how much these pathogenic pathways interact,” he added, “so if they’re causing disease in parallel and you treat one pathway, you still have the other pathways causing disease, and a single therapy won’t work.”

Also unknown: the stage at which these pathways cause disease. “The phase 3 trials have all targeted complement, part of the innate immune response, which is typically one of the first lines of defense,” said Dr. Handa. “Logically, you’d think [complement] would occur in early-rather than late-stage AMD, so it may not be the relevant target for GA.” To make substantive breakthroughs would mean prioritizing known pathways of disease and validating new, FDA-approved functional and structural endpoints for studies, he added.

Bright Future
Despite the unknowns, the future of GA treatment is bright, Dr. Lad said. “The science and the biomarkers have improved substantially in the past few decades.” In addition, she said, clinicians will be able to target pre-GA lesions to prevent functional loss, as the imaging of early disease has substantially improved. “All of these new advances will help patients going forward.”

Meet the Experts

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See disclosure key, page 8. For full disclosures, see this article at aao.org/eyenet.