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GA Perspectives: Patients Experiencing Difficulties With Reading and Driving

Dr. Chang:
Hi. My name is Margaret Chang, and I am a retina specialist from Sacramento, California.

Color fitness fundus photography has been used as the gold standard for defining and grading geographic atrophy for many decades. It is usually seen as a sharply demarcated area of RPE hypopigmentation with increased visibility of underlying choroidal blood vessels. However, depending on whether there is medial opacity and depigmentation of the RPE, subtle changes can be difficult to identify, especially over time. We now use multimodal imaging to commonly define areas of geographic atrophy, and one of the most useful tools is fundus autofluorescence. On FAF, GA lesions appear as decreased autofluorescence or hypo-autofluorescence due to the loss of RPE cells that contain lipofuscin molecules that normally fluoresce. FAF is currently the modality accepted by regulators, such as the European Medicine's Agency and the FDA for clinical trial registration.

Geographic atrophy growth rates can differ depending on the extent and pattern of hyper-autofluorescence on FAF. Absence of hyper-autofluorescence, or focal patterns of hyper-autofluorescence often correlate with slow GA growth rates. Diffuse and banded patterns often have greater than double their growth rates, and the diffuse strickling subtype pattern has the highest growth rate of all. One drawback to FAF is that it can sometimes be difficult to determine whether there is foveal involvement, because the fovea is normally hypo-autofluorescent due to the high concentration of light-absorbing xanthophyll pigment. In these cases, correlation with other imaging modalities can be helpful.

Near infrared reflectance imaging is one such modality. We often obtain these images at the same time as Heidelberg Spectralis OCT images. NIR is used with longer wavelength than that used by fundus autofluorescence. It is relatively easy to obtain through smaller pupils, and the longer infrared wavelengths are not as impeded by medial opacity. Now, since GA lesions do appear brighter than non-atrophic areas, it can be easier to determine foveal boundaries as demonstrated here. However, the contrast quality between atrophic and non-atrophic areas is diminished in eyes with thinner choroid, and variability between images can lead to difficulty to quantify lesions over time.

We now use OCT as a common way to define areas of geographic atrophy. There were previously multiple definitions of GNP-GA lesions, but a consensus group, the CAM group, developed a consistent new way to define atrophy and OCT as correlated to other multimodal imaging findings. The OCT correlate of geographic atrophy and macular atrophy is complete RPE and outer retinal atrophy, or cRORA.

Now, in order to meet the cRORA classification, a lesion must have three characteristics; choroidal hyper-transmission of at least 250 microns, RPE cell loss, and loss of all outer retinal layers all in the absence of an RPE tear. cRORA can occur in the context of non-neovascular AMD, in which case we call it geographic atrophy. Or it can also occur in eyes with previous or coexisting CMB, in which case we prefer the term macular atrophy.

An earlier stage of atrophy is incomplete RPE and outer retinal atrophy, or iRORA, in which case some cRORA, but not all of the cRORA criteria are met. As it turns out, there is good correlation between geographic atrophy measured by FAF and geographic atrophy measured by OCT, with FAF giving slightly consistently larger measurements than OCT in the same subjects.

Now, as we have more advanced software technology, GA area measurements are likely to become more sophisticated. But at this time, it can require more user input to measure lesion size on FAF, while multiple groups are testing automated deep learning-based algorithms for GA segmentation and area quantification OCT. These AI grading systems have been validated and compared to experienced graders and found to reliably segment GA area on OCT with high accuracy. This is more important as we have more clinical trials for GA to slow progression rate, and more therapies are currently being marketed. However, there's are not currently clinically available.

My case is that of an 86-year-old pseudophakic Caucasian woman who first presented to me with some non-specific visual complaints of problems reading and blurred vision in 2017. Her vision at the time was 20/30. Since then, although she has maintained her vision. She complains of progressive problems reading and watching TV, especially when she is trying to follow the ticker tape at the bottom of the screen.

She was very interested in enrolling in clinical trials for one of the GA therapies, but unfortunately, due to her cardiac history, she was never able to be enrolled. However, she is desperate to start treatment. This is her fundus autofluorescence and fluorescein angiography from 2017. As you can see, she has significant GA areas great in the left eye than in the right, with some hypo-autofluorescence surrounding the areas of GA. This OCT scan from 2017 shows the area of cRORA in the right eye with complete RPE loss and choroidal hyper-transmission, and loss of outer retinal layers measuring greater than 250 microns.

We can see quite clearly on the colors taken in 2023 that lesions in both eyes have grown significantly in the last 6 years, and that although she maintains 20/30 central vision, she is really just seeing through an island of tissue in both eyes. Now, this is the fundus autofluorescence. As we previously discussed, it is difficult to determine whether there's foveal involvement just on the FAF, because the fovea is also dark. However, you can see from the color images that the fovea has not been involved and the vision is also good. So, it is difficult to judge this based on FAF alone. Near infrared and OCT images demonstrate the foveal sparing with larger areas of cRORA.

This summary slide shows the progression in GA in both eyes leading to decrease in functional vision, with preservation of central visual acuity measurement in the past 6 years in both eyes.

We all know that macular degeneration is a growing worldwide problem. As the population ages and grows, the number of people affected worldwide is projected to increase from 186 million to 288 million in the year 2040. Currently, 5 million people worldwide are affected by geographic atrophy. Eighty-five to 95% of people with a AMD have the dry form, and of those 30% will progress to have the advanced form of dry AMD called geographic atrophy. Now, GA is characterized by a loss of RPE and photoreceptors and leads to a dense, irreversible scotoma in affected areas.

Although age and genetics, along with modifiable risk factors such as smoking, are the most important risk factors for macular degeneration, it seems clear that in terms of the pathophysiology of geographic atrophy, the complement system plays and important role. Complement is the first line of defense of the immune system. It protects us against microorganisms and is not adaptable or changeable as we age. The complement cascade can be activated through three different pathways: the classical, the alternative, and the lectin pathways.

The classical complement pathway is triggered by the antibody bound to antigen, while the lectin pathway is activated by carbohydrates and oxidative stress. The alternative pathway can be activated spontaneously for immediate immune response, but it is usually triggered by microbial pathogens, cell debris, or molecular aggregates. These pathways involve proteins that mostly exist as inactive precursors that are then sequentially cleaved and activated. All of these pathways converge at C3, which is the most abundant complement protein found in the blood, which then results in the formation of the activation products C3a, C3b, C5, and the membrane attack complex. The end result of complement activation is cell death and inflammation.

Now, two different complement inhibitors, pegcetacoplan, which targets C3, and avacincaptad pegol which targets C5, have shown positive Phase 3 results for the treatment of geographic atrophy. Pegcetacoplan was FDA approved in February 2023, while the FDA decision on avacincaptad pegol should be forthcoming shortly.

We'll now go over some of these pivotal Phase 3 studies. The Phase 3 DERBY OAKS trial of pegcetacoplan were two identical multicentered trials enrolling a total of 1,258 patients. Patients were randomized to pegcetacoplan 15 mg given monthly or every other month, or ham monthly or every other month. While the primary endpoint was the change in total area of GA lesions at 12 months, patients were followed for a total of 24 months. Patients are followed for up to 3 years in GALE extension study.

These trials had quite broad inclusion criteria allowing patients with foveal and non-foveal GA, and also allowing fellow eyes of those with CMB. GA lesions had to have evidence of perilesional hyper-fluorescence in order to qualify for inclusion. At 2 years, patients in both DERBY and OAKS saw a decrease in rate of GA growth in both groups ranging from 18 to 22% in the monthly treated group, and

17 to 18% in the group treated every other month. The effect of pegcetacoplan was seen to increase over time.

Of particular note, we're going to discuss the risk of CMB in these groups. Pegcetacoplan treatment did seem to increase the risk of CMB in treated patients. 3% of sham-treated patients in DERBY and OAKS developed CMB at 2 years, while 12% of patients treated every month with pegcetacoplan, and 7% of patients treated every other month, developed CMB at 2 years.

We'll now go over the avacincaptad pegol trials. GATHER1 enrolled 286 patients in two phases of the trial, each testing two different monthly doses of ACP versus sham. The primary endpoint was the mean change in GA area from baseline to month 12 using a square-root transformation, but patients were followed out to 18 months. In GATHER2 448 patients were randomized to monthly 2 mg ACP or sham. The primary endpoint was the mean rate of growth in GA area as measured by the slope of GA growth from baseline to month 12. In year two, patients in the ACP arm were randomized to monthly or bimonthly treatment, and the sham treatment group continued on to sham. In both studies, patients were eligible only if the GA was within 1,500 microns of the foveal center but did not involve the center itself. Patients with CMB in either eye were excluded from the ACP trials.

The mean observed GA growth from baseline to 12 months was statistically significantly reduced in the ACP 2 mg groups compared to sham in both GATHER1 and GATHER2 with a 27.4% reduction versus sham at 1 year for the GATHER1 trial, and a 14.3% reduction versus sham at 1 year for the GATHER2 trial. As in the pegcetacoplan trial, the rates of CMB were higher in the ACP treated patients. At 1 year, 2.7% of sham patients in the GATHER1 trial, and 4.1% of sham patients in the GATHER2 trial developed CMB. The risk was 9% for the GATHER1 trial ACP treated patients, and 6.7% for the GATHER2 ACP patients.

Now, what is the true rate of CMB occurrence in GA eyes? Previously, different studies have found rates ranging from 3.4% to 20%. Now, most of these had relatively small sample sizes, and the populations examined likely differed between studies. We can see from the sham groups in the pegcetacoplan and avacincaptad pegol studies that the rate is likely actually on the lower end of the spectrum.

This is the case of an 87-year-old pseudophakic Caucasian woman who was initially referred by her optometrist for a baseline macular degeneration evaluation in 2015. The patient had minimal symptoms at the time. She was re-referred to us in 2023 with increasing distortion in both eyes and difficulty driving. We see in two – we see in these images in 2015. OCT and near infrared images show small, isolated lesions and drusen in both eyes. Fundus autofluorescence did not show significant hypo-autofluorescence around the atrophic lesions. You also see the lesions quite nicely here on near infrared and FA as well.

Here are the OCT and near infrared images from 2019. Her vision has dropped in the right eye, and she is complaining of glare and increased distortion. The atrophic lesions have increased in size, but we thought that her symptoms were from cataract and referred her for a cataract surgery.

Here are the autofluorescence and fluorescein images from that year.

She now came back to our office in 2023 with decreased vision, 20/70 in the right and 20/100 in the left. She had been diagnosed by an outside physician with CMB in her right eye in 2021 and has been maintained on 10 to 12-week aflibercept injections in the right eye. Her main complaint now is distortion and difficulty driving. On FAF you can see much larger areas of geographic atrophy, and hyper-autofluorescence around her areas of GA, suggesting that she is at a higher risk of further progression.

This is a summary slide showing the growth in GA from 2015 to 2019, with an acceleration of growth to 2023.

I think that there are several important issues to address with this case. Number one, she came in with subjective visual problems with distortion and difficulty driving. Addressing the problem of driving together with the patient and the family and discussing whether the continuation of driving is truly best for the patient is an important first step, along with an updated refraction and low-vision evaluation for optimal visual aids. Number two, discussing therapy with complement inhibition is important. The left eye may have a greater risk of CMB conversion given the history of concomitant CMB in the right eye and needs to be monitored closely. The right eye is on a 10 to 12-week schedule for anti-VEGF therapy, so the preferred treatment schedule for complement inhibition may not match the anti-VEGF therapy treatment schedule. It can be difficult for the patient to come back for all of her injection visits, especially if she does not wish to come back for the injections for the same eye on the same day.

It is also difficult for the retina specialist in the office to make all of these appointments possible for all of their patients given the high treatment burden that their patients need already with anti-VEGF therapy.

We are at a truly remarkable point in our field where these questions are able to be asked. Thanks for joining us.