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RT Retina Today

UPDATE ON GEOGRAPHIC ATROPHY AND COMPLEMENT SYSTEM-BASED THERAPEUTICS

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Update on Geographic Atrophy and Complement System–based Therapeutics

CONTENT SOURCE

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

ACTIVITY DESCRIPTION

The impact on quality of life for patients with geographic atrophy (GA) is significant. This supplement reviews the prevalence of age-related macular degeneration (AMD), including advanced AMD (exudative and GA) as well as the pathogenesis of GA and the complex role of the complement system in GA development. The faculty members also discuss the latest clinical trial data for pipeline candidates targeting the complement pathways for the treatment of GA.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists who treat patients with retinal diseases.

LEARNING OBJECTIVES

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

- **Describe** the prevalence of advanced AMD, including advanced AMD (exudative and GA)
- **Explain** the pathogenesis of GA
- **Understand** the complex role of complement system in GA development
- **Outline** pipeline candidates targeting the complement pathways that are under investigation for the treatment of GA

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for CME Credit.

1. Please rate your confidence in your ability to understand the complex role of the complement system in geographic atrophy (GA) development (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. Globally, there are about _____ people with GA.

a. 1 to 3 million
b. 3 to 5 million
c. 5 to 7 million
d. 7 to 9 million

3. For patients with GA, _____ is reduced even when _____ remains good.

a. Contrast sensitivity; visual acuity
b. Visual acuity; contrast sensitivity
c. Lesion growth; visual acuity
d. Contrast sensitivity; retinal pigment epithelium

4. According to a meta-analysis by Shen et al, what is considered to be a "significant prognostic factor" for the GA effective radius growth rate?

a. Baseline size
b. Change in size after 6 months
c. Location relative to the retinal pigment epithelium
d. Lesion focality

5. Which classification scheme defines atrophy based on the specific retina layer involved?

a. Age-related Eye Disease Study
b. Simplified Age-related Eye Disease Study
c. Beckman Institute
d. Classification of Atrophy Meeting

6. If Mrs. Jones presents with reticular pseudodrusen and no apparent atrophy, but complains of poor vision under mesopic conditions despite being 20/20 in your office, what are some assumptions you might make?

a. The retinal pigment epithelium layer is likely still functioning properly
b. The photoreceptors are damaged
c. Foveal involvement is unlikely
d. Atrophy development is slow

7. The complement pathway is _____

a. Involved in the pathogenesis of GA
b. Decreased in the serum of patients with age-related macular degeneration
c. The only pathway that can potentially slow GA progression
d. Not a viable target for downstream regulation

8. Which of the following is a complement factor C5 inhibitor?

a. Pegcetacoplan
b. MC-1101
c. Avacincaptad pegol
d. Photobiomodulation

9. Which of the following is a complement factor C3 inhibitor?

a. Pegcetacoplan
b. MC-1101
c. Avacincaptad pegol
d. Photobiomodulation

Update on Geographic Atrophy and Complement System–based Therapeutics

Over a 15-year period, the estimated incidence of progression from early AMD to geography atrophy (GA) is almost 14%.[1] Recent studies estimate GA affects more than 5 million patients worldwide, with more than 1 million affected in the United States alone,[2-4] and there are no approved therapeutics available to treat the disorder. That may change in the not-so-distant future, as clinical trials that are evaluating complement factors are progressing from phase 2 to phase 3.

Evolve Medical Education brought together leading experts from across the globe to talk about the topic of GA. Here are their thoughts.

— Peter K. Kaiser, MD, Moderator

Q | Peter K. Kaiser, MD: How do you describe GA to your patients?

Frank G. Holz, MD: I explain that we have cells in the retina, and that the light-sensitive cells—the photoreceptor cells—are dying. It's a process of neurodegeneration, and then the cells simply die. Once they degenerate, they do not rejuvenate. This is the natural history of nonexudative age-related macular degeneration (AMD) in its late stage.

Dr. Kaiser: Dr. Loewenstein, numerous entities have looked at classifying GA. Can you elaborate on some of those classification schemes?

Anat Loewenstein, MD, MBA: The first classification was the Age-Related Eye Disease Study (AREDS).[5-7] In the early 2000s, the classification was really rather complicated and gave scores for every feature. But in 2005, AREDS simplified itself in Report Number 18.[8] In that classification, the researchers looked at color fundus photos to detect two features (drusen and pigment abnormalities) and scored them on a scale of 0 to 4 to determine the approximate 5-year risk of developing advanced AMD.

The Beckman Institute[9] also looked at progression to advanced AMD and used fundus photography. Table 1 shows their AMD classifications, but it wasn't much different from the AREDS classification.

I think the major breakthrough for clinicians was the Classification of Atrophy Meeting (CAM) in 2017.[11] That group defined atrophy based on the specific retina layer involved. First, the group classified the atrophy as complete (C) or incomplete (I), and whether it is on the outer retina. The CAM group Report No. 5 was published last year[12] and recognizes the exact optical coherence tomography (OCT) features on a continuum basis from early to late AMD. Each of these classifications has advantages and disadvantages, but I think the most acceptable one is the latest one: the CAM classification.

TABLE 1. BECKMAN INSTITUTE'S PROPOSED AMD CLASSIFICATION.[9,10]

Classification of AMD	Definition (lesion assessed within 2 disc diameters of fovea in either eye)
No apparent aging changes	No drusen and No AMD pigmentary abnormalities*
Normal aging changes	Only small drupelets (small drusen ≤ 63 μm in diameter) and No AMD pigmentary abnormalities
Early AMD	Medium drusen > 63 μm and ≤ 125 μm and No AMD pigmentary abnormalities*
Intermediate AMD	Large drusen >125 μm and/or Any AMD pigmentary abnormalities*
Late AMD	Neovascular AMD and/or Any GA

*AMD pigmentary abnormalities=any definite hyper- or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities.

Q | Dr. Kaiser: Prof. Monés, you and Prof. Holz were part of the CAM group. What specifically made the group decide to create another classification scheme, and can you explain the new classifications of incomplete retinal pigment epithelial (RPE), outer retinal atrophy (iRORA), and complete RPE outer retinal atrophy (cRORA), as well as incomplete outer retinal atrophy and complete retinal atrophy?

Jordi Monés, MD, PhD: The issue for me is that the old classifications did not distinguish different pathways. The mechanics of the atrophy and the dynamics of the atrophy differ significantly. Let's take the example of reticular drusen or soft drusen in intermediate AMD. The photoreceptors may atrophy before the RPE in reticular drusen. That is an important concept to recognize because the prognosis and visual function deterioration can differ significantly between patients. We need to distinguish phenotypes.

Second, we traditionally divided AMD into early, intermediate, and late, and then subdivided late into exudative or atrophic, but those are two different pathways. End-stage AMD is always

atrophic AMD. The eye attempts to compensate for that degenerative process by creating new vessels. When the neovascular process takes over, the eye doesn't have time for atrophy because now there is a disciform scar and fibrosis. It's not a divergence between the two pathways. There is only one path to atrophy and people may or may not develop new vessels during the process.

Dr. Kaiser: Dr. Khanani, as a busy retinal physician, do you use any of these classification schemes when you see a patient with GA? How do you use these classification schemes to determine your follow-up (or to enroll patients in a study)?

Arshad M. Khanani, MD, MA: That's a great question because at this point, we do not have any treatment for patients with GA. The differences between iRORA and cRORA do not really matter from the patient's perspective. From our perspectives, however, we know if they have cRORA they will progress faster; we know if it's closer to the center they risk vision loss. Dr. Loewenstein explained these classifications very well, and I think they're practical.

Kudos to Drs. Holz and Monés (and others) for the CAM classification, as that has provided us with some biomarkers we can use to assess and predict progression.

I certainly use the CAM classification when I'm enrolling patients in clinical trials. By using the definitions and geographic markers as laid out by the CAM group,[12] I'm able to look at the features and better classify the patient's disease. Once we have approved treatments, I'm hopeful we will be able to intervene early enough in the disease course that we won't have patients with cRORA.

INCREASING PREVALENCE

Dr. Kaiser: Some recent reports in the literature have shown eyes with multiple large drusen (>125 µm) are more likely to develop GA than eyes with smaller drusen (<63 µm) [15-year odds ratio (OR), 14.5, 95% confidence interval (CI) 5.9-35.7; 10-year rate in 75- to 80-year-olds, 26%]).[3,13,14] Some natural history studies suggest differences found in lesion progression rates can be stratified by hyperfluorescence patterns.[15] More recently, Shen et al reviewed 12 studies (3,489 eyes) and determined lesion focality is a significant prognostic factor for the GA effective radius growth rate.[16] The PROXIMA A and B studies found adjusted mean (standard error) change in GA lesion area from baseline was 3.87±0.15 mm^2 in participants with bilateral GA (Proxima A), 3.55±0.16 mm^2 in the fellow eye CNV cohort (Proxima B), and 2.96±0.25 mm^2 in the fellow eye intermediate AMD cohort (Proxima B).[17]

Q | **Dr. Kaiser:** Prof. Holz, you are part of a large group in Europe that is looking at the prevalence of atrophy as well.[18] What is your perspective on why prevalence numbers are so difficult to ascertain in this disease?

Prof. Holz: That's an excellent question, because the published epidemiological studies use different definitions of atrophy. Some used a minimum size or only used color fundus photography, whereas others use high-resolution imaging including scanning laser ophthalmoscopy and OCT, all of which means the numbers from all these studies differ. We recently conducted a meta-analysis in Europe, where 67 million people are affected by any stage of AMD.[18] Even those with early and intermediate AMD will progress, and as Prof. Monés pointed out, if they live long enough they will develop GA. The number of people with late-stage disease is somewhat smaller; globally the estimate is about 5 to 7 million individuals with actual GA.

Regardless of what the numbers currently are, we know that they are increasing exponentially with age. Given our increasing longevity, there is no doubt in my mind that the prevalence and incidence will continue to rise.

Dr. Kaiser: Prof. Holz brings up a good point about the diversity in definitions underscoring the prevalence data. I was looking at data from Asia,[19,20] and thought the numbers couldn't be correct. In China, for example, the prevalence of GA was 0.15% (95% CI = 0.05-0.47) in people age 45 to 49 years and 1.09% (95% CI = 0.35-3.36) in those age 85 to 89 years.[19]

But part of the difficulty in determining prevalence is that in the absence of treatment, many of these patients either are not seen or referred for evaluation. These older patients are being seen by multiple health care providers, from primary care doctors to optometrists to general ophthalmologists, and finally, retina specialists. In countries like China, for instance, there are simply not enough retina specialists needed to evaluate all the patients with GA when there is no treatment. I believe those numbers may be artificially low and will increase as soon as we get an approved therapy. Dr. Loewenstein, what about quality of life? Some of my patients with extrafoveal disease have an excellent quality of life, but as they progress and become closer to the center of the fovea, their quality-of-life decreases. What do you notice in your patients in terms of progression of the symptomatology of atrophy?

Prof. Loewenstein: Let me divide my response into two. You've made a very valid point Dr. Kaiser. In many of my patients, the visual acuity (VA) is good because the atrophy hasn't yet reached the fovea, or at least not that I can see even with all the multimodal imaging I'm using. But a lot of those patients will complain that they can't see, or cannot read, or cannot detect details. The way that GA impacts my patients' quality of life is much greater than what I can detect with VA.

There are several studies that underscore these observations by analyzing a patient's reported outcomes by way of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25).[21-24] Patients have really poor scores, despite the good VA; those scores are correlated with reading speed and microperimetry. Modalities aside from VA might be almost normal until very later stages of the disease. For example, contrast sensitivity in patients with GA is reduced, even when VA remains good.[25-27]

Low-luminance contrast sensitivity also impacts quality of life. Ou et al recently published a study that concluded the interaction

between luminance and VA and luminance and contrast sensitivity are different and impact vision differently.[26] I find that in my patients as well; quality of life is significantly disturbed in patients with GA.

NATURAL HISTORY AND PROGRESSION TO LATE AMD

Q | Dr. Kaiser: Prof. Monés, what is the natural history as we move from early to intermediate to late AMD?

Prof. Monés: In intermediate AMD, often there is soft drusen under the RPE, and the RPE stays quite intact and functioning for long periods. In this subgroup of patients, atrophy development is slow. But with reticular pseudodrusen, even without apparent atrophy, the photoreceptors are damaged. These patients complain of visual impairment in mesopic conditions despite having 20/20 vision in the office.

Patients with pure intermediate AMD differ depending on the type of drusen. When atrophy starts, it is secondary to soft drusen, but again, you have pinpoints of atrophy different places, and this tends to progress slowly. But with reticular drusen, and atrophy secondary to that, the enlargement rate may be unexpectedly quick. But because patients may have good VA, they have a false sense of good visual function. So when the atrophy progresses, it drives my patients crazy—they can go from 20/20 to 20/800 in 5 years. That's the devastating part of this disease—patients will go from great vision to a completely devastated macula in a really short amount of time.

For me, that's why it's so important to distinguish the phenotypes. A patient who takes 10 years before the atrophy progresses significantly is very different from the one I just described. That will also have implications, not only from a treatment perspective, but in how we counsel our patients.

RISK FACTORS

Q | Dr. Kaiser: Dr. Khanani, let's talk about modifiable and nonmodifiable risk factors. What are the main risk factors you discuss with your patients?

Dr. Khanani: One of the first things I start with is telling them I cannot stop the aging process. We know that after age 50, the prevalence of AMD quadruples with every additional 10 years of age.[13,17,18,20,28] I tell them I cannot change their genetics. But I also tell them what we can modify are their social and environmental risk factors, like smoking and dietary concerns.

The study of genetics is crucial right now. A recent study found two gene loci with genome-wide significance: protein arginine methyltransferase 6 (chromosome 1) and lanosterol synthase (chromosome 21).[29] The EYE-Risk group identified three GA subgroups that differed by genotype.[30] Our hope is that one day, sooner rather than later, we're going to have a treatment that can slow this disease down, and it will likely be based on genotype.

Dr. Kaiser: The complement cascade is considered a key component of the formation of GA. Prof. Monés, how do you view the complement pathway? Where is it in the pathology of macular degeneration? Is it the chicken or the egg? Or is it an innocent bystander?

Prof. Monés: Complement factor is a very complicated cascade; it's like having a truck with 20 brake pedals and 20 accelerator pedals. AMD is a very complex disease that encompasses exudative stress but also inflammation.[3,31-33] The inflammatory component is chronic, and the body has mechanisms to prevent the inflammation, but in GA, the complement factors are not in equilibrium. So there is an abnormal state of inflammation or an abnormal state of being unable to handle this low-grade chronic inflammation. And those processes take over eventually.

We need to remember this is a genetic predisposition from birth that does not manifest until a certain age. Other factors are implied, so complement is not the only factor, but it is certainly an important one.

By preventing the low-grade chronic inflammation, we may modify the progression of the disease and may be able to modify the time that patients lose vision. It's a very complex process with multiple steps in the complement pathway involved. The therapies we are investigating address some of these issues at the end of the cascade, so it may not be relevant to know which levels are normal. At the end of the complement cascade, you want to prevent those complexes and inflammatory proteins.

Dr. Kaiser: The complement cascade is our defense against bacteria and foreign invaders. Prof. Holz, which activator pathway of the complement cascade do you think is the most relevant for age-related macular degeneration?

Prof. Holz: In the innate defense mechanism, it seems that the alternative pathway is an important one.[34-36] But the question becomes should you go further up or further downstream to inhibit the complement attack against the aging macula? There are complement proteins associated with the early and intermediate stages of the disease. As Prof. Monés said, we have learned that these appear to have an impact on the onset of disease. There are some polymorphisms in risk alleles for the complement system that may also impact the speed of the lesion growth over time in GA patients.

Dr. Kaiser: One of the big issues for me is that the clinical studies evaluating GA progression by modulating the complement cascade may be too late. If we really want to attack dry macular degeneration, we need to address it earlier in the disease state. What we don't know yet is how much earlier do we need to be to be successful. The second issue for me is that a lot of complement is produced locally, but some is produced systemically. I think it remains a large unknown as to where the best place to attack the complement cascade may be.

DIAGNOSIS AND EVALUATION

Q | Dr. Kaiser: Prof. Loewenstein, when patients are in your office with dry macular degeneration, what are some of the imaging modalities you use for diagnosis and evaluation?

Prof. Loewenstein: I examine them clinically (using the older definitions and grading systems). But those cannot evaluate the majority of lesion characteristics. I think autofluorescence is better and provides us with greater accuracy for lesion borders. It remains difficult to estimate foveal integrity with autofluorescence. So, we also look at the OCT and use the CAM classifications.

I do think when we talk about OCT-angiography, we are possibly seeing the loss earlier than when we see it clinically.

While this is not clinical everyday work, we know there are artificial intelligence (AI) tools now being developed to assess the importance of these diagnostic parameters.[37,38]

Q | Dr. Kaiser: Prof. Holz, do you use the classification schemes to predict prognosis? How do you talk to your patients when they have a pattern that may be more worrisome?

Prof. Holz: The pattern can basically tell you how sick the still-viable retina is in the surrounding areas of "bad" retina. Since we do not have a treatment, I don't go into details with patients as it doesn't affect how I manage them; I don't see them sooner or more frequently. But once these emerging treatments come to market (hopefully), then the patterns will take on more significance.

For example, if someone has a parafoveal atrophic patch that is close to the fovea, then I would urge him to have the treatment, and the sooner the better. If I detect a patch way out of the macula, I may be more relaxed and that atrophic lesion would take some time before it became vision-threatening.

It's important for all of us to be aware of factors that impact progression rates. When we have treatment available, this will surely impact how we manage these patients.

Dr. Kaiser: In clinical studies, we use a lot of diagnostic and imaging modalities, including microperimetry, low-luminance vision, and reading speed, that are not routinely used in clinical practice. For instance, low-luminance vision is oftentimes affected much more than best-corrected VA.[21,25,26] Are any of these tests important to your practice? Or are they really just for clinical studies?

Prof. Monés: That's a very tricky and complicated question because sometimes we confound real practice with practicability. If we want to address the functional state of these patients, we need to address functional tests. Unfortunately, VA—which is the most important variable we can measure—is not terribly useful here. If we want to quantify color or microperimetry, that can often be difficult for patients and may not be reliable. If patients are presenting with 20/20 vision but complaining they can't see, that's what matters. Contrast sensitivity testing can take 2 to 3 hours, and patients need to come twice because it can be so tiring for them. We need to find a way to measure function; when we measure GA by its boundaries we extrapolate a functional impact, but it's not direct. We need to know which patients would benefit from temporal monthly injections; before we can justify that invasive kind of intensive therapy, we need to know the patient will maintain a state of functional vision.

In a lot of practices, these are the patients who are forgotten because we have nothing to help. We're talking about a massive amount of people. In well-developed countries, life expectancy is increasing, so the prevalence of GA is also rising, as we've discussed. In the 21st century, it's difficult to explain to patients that we don't have anything to help them. People don't understand that.

Dr. Khanani: I agree with Prof. Monés about needing a functional test. None of the tests we have now are practical. Microperimetry takes hours. Low-luminance vision testing, reading speed, all of them take a long time. And in a busy clinic, that's just not practical. We treat patients to the OCT, just as we do with wet AMD. Fundus autofluorescence and OCT will be a way to monitor these patients. We need some parameter of functional aspect that is easy to administer and not time-consuming.

Dr. Kaiser: That's a good point. In general, I'll do a fundus autofluorescence and an OCT to make sure there's no subclinical choroidal neovascularization (CNV) that I may be missing. But all the other testing, in my opinion, is really for research purposes.

POTENTIAL TREATMENT MODALITIES

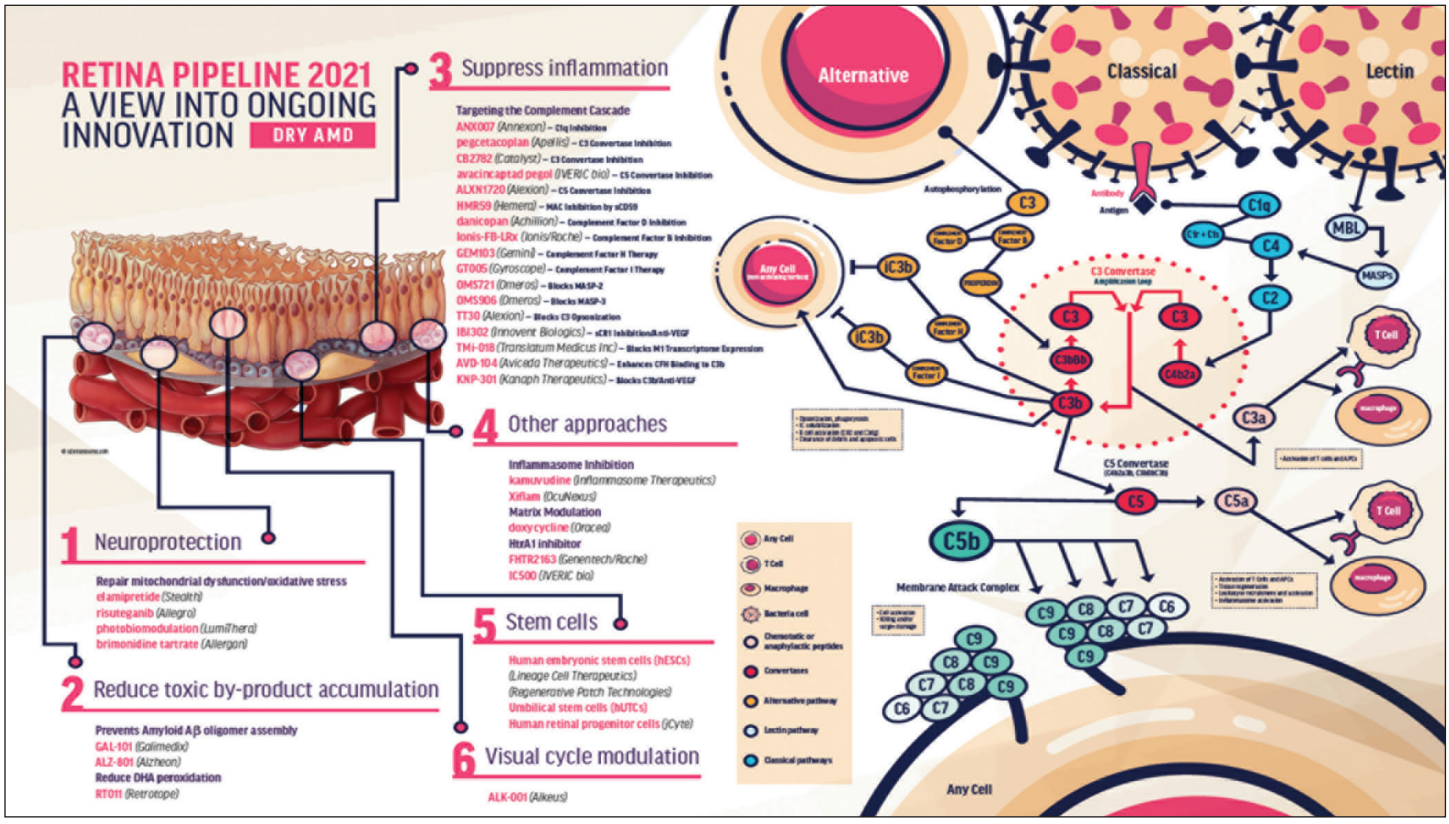
Dr. Kaiser: When we think about dry AMD, the first "chapter" of treatment were things like antioxidants, vitamins, etc. But those are not successful at preventing GA. We tried using laser on the drusen, but that also proved unsuccessful. There is now a photobiomodulation laser that obtained a CE mark in the European Union for the treatment of dry AMD. The manufacturer notes that the laser works through the absorption of photons by photoacceptors in the targeted tissue, which then change signaling modalities after absorption.

Q | Dr. Kaiser: Does anyone have experience with this modality?

Prof. Holz: While it has a CE mark, evidence from large-scale prospective, randomized clinical trials are not yet available to demonstrate efficacy and safety.

Prof. Loewenstein: It's too early to tell if it will be successful.

Dr. Kaiser: The next "chapter" is looking at neuroprotection. We've had a lot of failures in neuroprotection, especially in glaucoma. Some companies are now researching how to reduce oxidative stress and repairing some of the mitochondrial dysfunction. Dr. Khanani, can you elaborate on some of these concepts?



Source: P. Kaiser, MD

Figure. The dry AMD/GA pipeline. Reprinted with permission from *Retina Today*.

Dr. Khanani: It's interesting because we're trying to intervene early and decrease the progression from intermediate AMD to GA. Obviously, we don't have a biomarker that can evaluate mitochondrial dysfunction and repairing oxidative stress. Functional endpoints are crucial here, all of which we talked about earlier.

Risuteganib has shown protective benefits against mitochondrial dysfunction and actin reorganization,[39] as well as oxidative stress.[40] The phase 2 intermediate dry AMD study met its primary endpoint, with 48% of patients in the risuteganib arm gaining at least 8 letters at week 28, compared to just 7% of patients in the sham arm at week 12 (at week 16, patients in the sham arm were crossed over).[41] Allegro was preparing to start a phase 3 in the fourth quarter of 2020, but to date, nothing is listed on Clinicaltrials.gov.

The BEACON phase 2b study evaluated a sustained-release intravitreal formulation of brimonidine as a treatment to reduce GA expansion rate, and it did slow down progression. This treatment significantly decreased GA growth by 10% (-0.36 mm^2, $P = .047$) at month 24 and 12% at Month 30 (-0.52 mm^2, $P = .017$). The effect size increased by 71% in the population with lesion sizes > 4.5 mm^2.[42,43] It's unclear where that program stands now that AbbVie bought Allergan.

Dr. Kaiser: Hopefully, it will move into phase 3. Brimonidine has been shown to be neuroprotective in numerous models. And certainly the phase 2 data looked pretty good, especially in the larger lesions. The Figure shows where research is ongoing for dry AMD.

One of the hallmarks of dry AMD is the formation of drusen. We've looked at trying to prevent some of this toxic, byproduct accumulation. It was fascinating to me to see the parallels between Alzheimer's disease and dry AMD.[44] That led to some companies evaluating their Alzheimer's drugs as a means of attacking beta-amyloid formation through antibodies. Those led to the findings that it's not the oligomer itself, it's the misfolding that is the toxic part in both Alzheimer's and drusen in dry AMD.

Prof. Loewenstein: Glatiramer acetate is used to target beta-amyloid, and looked as though it was very promising at first, with a reduction in drusen area.[45,46] But a larger phase 2 study showed no benefit. It made a lot of sense, though, because drusen really look like amyloid accumulation. But it wasn't as beneficial in GA or in drusen disappearance without the development of GA.

Dr. Kaiser: That's an unfortunate byproduct of a regulatory environment as well. Our regulators are going to allow us to get something approved based on VA, and if VA doesn't improve or if VA loss is not prevented, then we need to use these secondary outcomes. An acceptable outcome would be the prevention of atrophy progression, but many of these toxic byproduct drugs need to be given much earlier in the disease process. For us to prove the drug works may take years before any effects are noticeable. Retrotope's DHA analog would

reduce DHA peroxidation,[47] which is an early step that may cause some of the complement cascade to be activated, but evaluating it to prevent GA progression may be too late in the process.

Are there other approaches that are being looked at that you think are viable?

Prof. Monés: The inflammasome approach would be something relatively similar to the anticomplement in that it tries to prevent inflammation.[48-50] You rightly noted there is a lot of byproduct below and above the RP that becomes a vicious, toxic cycle. Trying to prevent these byproducts or targeting the inflammation makes a lot of sense. To my knowledge, though, no trial has shown advanced data.

STEM CELLS AND AMD

Prof. Monés: I'd like to talk about stem cells for a moment. I've had the privilege of seeing scans and OCTs on a project from Lineage Cell Therapeutics (US) in collaboration with Cell Cure (Israel). I can tell you that I've seen regeneration of the retina. That may sound too good to be true, but I checked and rechecked—new areas of external limiting membrane, new areas of photoreceptors above the RP. But we still need to figure out how to make this more consistent for more patients. I think this may open a door of hope, especially in cases that are too advanced and slowing the disease won't provide a benefit. We should keep an open mind about the stem cell approach for those patients.

Dr. Kaiser: One obstacle with injecting stem cells subretinally is that they need to be polarized, which some companies are pursuing. Others are looking at differentiated stem cells. Prof. Monés, can you elaborate on the differing approaches?

Prof. Monés: At this point, it's more theoretical than real. There was a theory that cell suspension would fail in Bruch membrane, and they would never polarize and form a monolayer. But I saw the exact opposite. If you have a suspension of cells, then the surgical procedure is much simpler than implanting a scaffold or implanting matrixes. Those are difficult. As retinal surgeons, we're used to injecting, so it really is a straightforward procedure. The cell purity is crucial no matter what procedure is being used. I would not rule out suspension of RPs; I think they may work very well.

Prof. Loewenstein: We're also a center for Cell Cure. What Prof. Monés said is very valuable. One thought about stem cells is that their main role might be a bit disappointing if it turns out they have a solely atrophic effect. That's yet to be proven. But if it is atrophic, then polarity does not matter as much. All of this still needs to be proven with larger numbers. The Cell Cure approach evaluated eight patients; that's too small to say anything definitive. But the possibility exists that polarization may not be necessary.

Dr. Kaiser: That would be wonderful.

TREATMENTS IN PHASE 3 STUDIES

Q | **Dr. Kaiser:** Let's turn our attention to the complement cascade and study drugs that are in phase 3. What did we learn from their phase 2 results?

Prof. Holz: There is a silver lining here in that we hope data from the phase 2 or phase 2/3 studies are promising. However, the caveat being that the MAHALO studies[51,52] on lampalizumab show positive signs that were not reproduced in the larger phase 3 trials on almost 2,000 patients.

Phase 2 data from both Apellis and Iveric Bio should be available this year. These trials are evaluating products that attack different complement proteins: C3 and C5. At this time, the jury's still out on which of these is optimal. We now know from the lampalizumab studies that inhibiting complement factor D is ineffective when locally administered. When we see hyperactivity of the complement system, we can measure it in patients with AMD in their systemic circulation (and complement factor is primarily produced in the liver).

Apellis' DERBY and OAKS phase 3 studies on pegcetacoplan are fully enrolled, and results from the phase 2 study showed pegcetacoplan significantly reduced the growth rate of GA lesions.[53] The phase 3 studies are 600-patient, prospective, international, multicenter, randomized, double-masked, sham-injection controlled phase 3 studies assessing the efficacy and safety of multiple intravitreal injections of pegcetacoplan in patients with GA secondary to AMD.[53]

Iveric Bio's avacincaptad pegol is a complement factor C5 inhibitor.[54] In its phase 2b study, avacincaptad pegol reduced the mean rate of GA growth over 12 months by 27.38% in the 2-mg group (P = .0072) and 27.81% in the 4-mg group (P = .0051) compared to the sham arm.[54,55]

These are two very promising clinical developments and it would be an important breakthrough because we have no treatment for the AMD subphenotype. It would be clinically meaningful if we can preserve the fovea for some years longer than compared to natural history.

Dr. Kaiser: Is there any concern about blocking C3 convertase or C5 convertase that we're essentially blocking the entire complement cascade, compared to blocking C1q inhibitor, which is much more precise?

Dr. Khanani: We initially had infection concerns about a panblockade of any of the three pathways. That's why Genentech opted to evaluate the alternate pathway with lampalizumab. We have two large datasets now from the FILLY trial (pegcetacoplan) and the GATHER1 (avacincaptad pegol) that evaluated the complete blockade of the complement system and we have not seen a signal for increased infection or any other adverse event that would be of substantial concern. At this point, it appears that blocking the complement hyperactivity and slowing it down as much as we can may be the best way to treat GA. The GOLDEN

study (NCT03815825) is evaluating Isis 696844 (IONIS-FB-LRx), a subcutaneous injection of an antisense RNA against factor B that is currently in phase 2; we should see data later this year. When it's a systemic treatment, questions surrounding compliance and safety need to be addressed. I'm excited to see the data.

Putting a block on the complement system and returning it to a normal state is where complement factor H (CFH) and complement factor I (CFI) come into play. At this point, we have not seen any safety issues, but the data is still early.

We don't have efficacy data yet from the ReGAtta study, Gemini Therapeutics' phase 2a dose-escalation study on GEM103, a recombinant human CFH, and top-line data is not expected until mid-year.[56] That study is designed to evaluate safety and tolerability and intraocular pharmacokinetics, so it may not show efficacy data. We also do not have efficacy data from EXPLORE, Gyroscope Therapeutics' phase 2 study on GT005, a gene therapy aimed at increasing production of the CFI protein.[57] But the phase 1/2 FOCUS study on patients in the first four cohorts showed no dose-related trends in the frequency or type of adverse events and no GT005-related serious adverse event. Plus, interim results showed GT005 was well tolerated, showed sustained increases in vitreous CFI levels in the majority of patients, as well as decreases in the downstream complement proteins associated with overactivation of the complement system, and this was true even in patients who had rare variants in the CFI gene.[58]

From my clinical perspective, we have enough data to argue the fact that we should go for complement blockade if we can, but phase 3 data will confirm the efficacy and safety of this approach.

Prof. Loewenstein: The FILLY and GATHER1 studies showed some efficacy, but monthly injections for these patients can be problematic. These are not patients who have CNV and can notice daily changes in vision if they're not treated. Even though I'm very excited that we have some hope, I'm worried that the patients in the phase 3 studies are the most advanced—some of whom have no functional vision and, in addition, are going to need frequent dosing.

Dr. Kaiser: I hope these companies are working on sustained-release devices or polymers to deliver their product over a longer period of time.

Prof. Loewenstein: They will definitely need to have that.

Q | Dr. Kaiser: Dr. Khanani summarized some of the gene therapy studies from Gyroscope. Do you think that 10 to 15 years from now we're going to be routinely using gene therapy in dry AMD? What are your thoughts or concerns about the long-term results of gene therapy?

Prof. Holz: Gene therapy would be a potential promising approach, especially if we determine that we need to treat earlier to prevent intermediate AMD or progression to late stages. Patients who would need treatment in their early 50s aren't going to relish the idea of being injected for 30 or 40 years. The first gene therapy product, voretigene, seems to be showing no safety concerns, even after several years. That needs to be the next step, once efficacy and safety are shown.

Prof. Loewenstein: But we are worried about inflammatory and other side effects that can come from the gene therapies.

Dr. Kaiser: Dr. Khanani briefly touched on the somewhat surprising side effect of blocking C3 convertase and C5, and that was the increase in CNV conversions compared to controls. There was a slight difference in rates between the two studies, but both showed an increase over sham.[55-58] What are your theories as to cause?

Prof. Monés: That is not a black-and-white question. We all think of CNV as "evil" because of its propensity to cause visual damage and blindness. But if I have a patient with GA and a nonexudative type 1 lesion, I'm very happy. Those type 1 nonexudative lesions can prevent atrophy progression. They're compensating for the choriocapillaris that isn't functioning properly. In my experience in GA, a nonexudative CNV can be good news. It's the exudative lesions that are harmful.

We need to have an open mind about anticomplement therapy; we want those new vessels in GA because that's the only way the GA will not progress. If we could design new, nonexudative vessels, we would make them. Instead, we can use pharmaceuticals to create those new vessels. If anticomplement factor works, but the price is we have to treat CNVs, that's a price I can live with.

Prof. Holz: Dr. Kaiser, in some of these patients with pegcetacoplan treatment, there was no evidence of CNV. Ten patients had CNV evidence by angiography and the remainder did not. Could you consider mechanism of action whereby the integrity of the RPE gets lost or is this a nonneovascular exudative phenomenon?

Dr. Kaiser: I think that's exactly what some of those cases were. It's not the CNV that we're used to seeing in our wet AMD patients; typically there is massive exudation and extremely poor outcomes. In the pegcetacoplan study, most of the CNVs were relatively hard to discern but the researchers were actively looking since it was a clinical study.[59] Prof. Monés' comments are germane to this, which is that patients who had a "conversion" actually did very well. That has to be taken into account—it may be an adverse event, but is it truly adverse for the patient? More long-term study data will be needed to figure out that aspect.

Prof. Loewenstein: Let's also remember the patients being treated are also being monitored. While CNV is an important factor, baseline VA is the most important biomarker for final VA. The earlier we can detect lesions, the earlier we can treat them so they don't become problematic. Those lesions are treatable. So what we will find in the phase 3 trials may be that a greater percentage develop CNV, but it's still treatable.

Dr. Khanani: As I'm enrolling patients in GATHER2, I do let patients know there is a slightly higher chance of CNV formation, and that may mean exudative AMD, but we have treatments for that. These patients know what dry AMD or GA has done to them. Prof. Loewenstein brings up a good point about frequency of injections and if they don't notice an improvement, that's a concern. But if my patients have lost vision in one eye from GA, they're very compliant with the monthly treatment. Their other eye acts like a control. So far, I haven't had a significant number of patients dropping out in any GA trials. While there is a treatment burden, we have no treatments. But I don't think we can have patients being injected monthly for 10 years. We need to look at longer-acting delivery systems.

Prof. Loewenstein: Especially for a patient who has already lost vision from GA.

Dr. Kaiser: We also know from CATT, IVAN, and other studies that macular atrophy occurs with anti-VEGF therapy.[60-62] Will there be a role for complement inhibitors in combination with anti-VEGF in wet AMD?

Prof. Monés: The most important question is if macular atrophy is derived from the scarring process because of the destruction of the new vessels. Or is there pure GA because we are interfering with the new vessels below the RP or below the photoreceptors. It may differ depending on the phenotype of the lesions. When you treat type 2 or type 3 lesions, they may have progression of the atrophy. We will always question if that's induced or promoted by the anti-VEGF or if it's natural history. Type 3 lesions are usually reticular drusen and have a quicker progression of atrophy than type 1, for example. But we still need to be open minded because we need to face AMD as a moving, fluid thing. Exudation and atrophy can't be separated; they do the same things to the eye. When we treat the exudation, we need to be aware of which phenotype so we can be more or less aggressive.

SELECTING THE RIGHT PATIENT

Dr. Kaiser: Let's fast forward 5 years when the pandemic is presumably over. By then, we may have some complement inhibitors that are approved.

Q | **Dr. Kaiser:** Here are a few questions for you the panel: Who is your ideal patient? Let's say you have a patient with extrafoveal GA in one eye, some soft drusen in the fellow eye. How do you initiate the conversation of injections, especially if they're 20/20?

Prof. Loewenstein has touched on this already, but a patient who has central GA in one eye or extrafoveal GA in their fellow eye knows what's coming. They'll return for injections. Will our health care systems be able to support the tremendous cost?

Prof. Loewenstein: I think this is the most important question. In 5 years, we'll know which patients will progress fast based on the genetic variants. We will be able to tell patients that if they are not treated, they'll have a 90% chance of advancing central disease or another complication. I also believe we will know more risk factors.

Prof. Holz: For now, the morphological features outperform the genetic risk scores. But as artificial intelligence and deep learning progress, we may be able to determine the risk/benefit ratio of treatment versus no treatment.

Prof. Loewenstein: For now, there is limited use for genetic risk scores.

Prof. Monés: Genetics have a tremendous impact, but they explain about 50% of the story. The best determinant of progression is having a historical 6-month evaluation for every patient. Six months is not going to make a big difference in outcomes over the long term, so my recommendation is to take a baseline measurement, OCT, autofluorescence, and repeat it 6 months later. You'll have the perfect picture of the rate of progression.

Dr. Khanani: These treatments obviously are burdensome, but I agree with Prof. Holz's recommendations to target earlier and earlier for essential GA. My goal is to prevent vision loss in their good eye. Central GA with 20/200? The damage is already done, and I'm not interested in giving them monthly injections because I don't think it will help. In real-world settings, we're going to intervene much earlier in the disease compared with patients who are being enrolled in these studies.

Dr. Kaiser: I want to thank all of you for participating in this incredible overview about the treatment of GA. ■

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Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

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

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

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Describe the prevalence of advanced age-related macular degeneration (AMD), including advanced AMD (exudative and geographic atrophy [GA]).	_____	_____	_____
Explain the pathogenesis of GA.	_____	_____	_____
Understand the complex role of complement system in GA development.	_____	_____	_____
Outline pipeline candidates targeting the complement pathways that are under investigation for the treatment of GA.	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to understand the complex role of the complement system in geographic atrophy (GA) development (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. Globally, there are about _____ people with GA.

a. 1 to 3 million
b. 3 to 5 million
c. 5 to 7 million
d. 7 to 9 million

3. For patients with GA, _____ is reduced even when _____ remains good.

a. Contrast sensitivity; visual acuity
b. Visual acuity; contrast sensitivity
c. Lesion growth; visual acuity
d. Contrast sensitivity; retinal pigment epithelium

4. According to a meta-analysis by Shen et al, what is considered to be a "significant prognostic factor" for the GA effective radius growth rate?

a. Baseline size
b. Change in size after 6 months
c. Location relative to the retinal pigment epithelium
d. Lesion focality

5. Which classification scheme defines atrophy based on the specific retina layer involved?

a. Age-related Eye Disease Study
b. Simplified Age-related Eye Disease Study
c. Beckman Institute
d. Classification of Atrophy Meeting

6. If Mrs. Jones presents with reticular pseudodrusen and no apparent atrophy, but complains of poor vision under mesopic conditions despite being 20/20 in your office, what are some assumptions you might make?

a. The retinal pigment epithelium layer is likely still functioning properly
b. The photoreceptors are damaged
c. Foveal involvement is unlikely
d. Atrophy development is slow

7. The complement pathway is _____

a. Involved in the pathogenesis of GA
b. Decreased in the serum of patients with age-related macular degeneration
c. The only pathway that can potentially slow GA progression
d. Not a viable target for downstream regulation

8. Which of the following is a complement factor C5 inhibitor? Pegcetacoplan

a. MC-1101
b. Avacincaptad pegol
c. Photobiomodulation

9. Which of the following is a complement factor C3 inhibitor?

a. Pegcetacoplan
b. MC-1101
c. Avacincaptad pegol
d. Photobiomodulation

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____ No

Probability of changing practice behavior based on this activity: _____ 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

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

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

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address: _____

_____