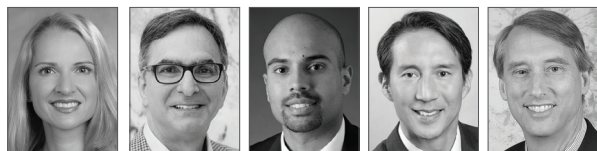


GEOGRAPHIC ATROPHY TREATMENT PEARLS

Experts share their insights on caring for a whole new patient population with newly approved therapeutics.

A CONVERSATION WITH ELEONORA M. LAD, MD, PHD; JEFFREY S. HEIER, MD; AND DILSHER S. DHOOT, MD
MODERATED BY ALLEN C. HO, MD, AND ROBERT L. AVERY, MD



The FDA approval of pegcetacoplan (Syfovre, Apellis Pharmaceuticals) for the treatment of geographic atrophy (GA) secondary to AMD is a milestone. We've had clinical trials for GA that have failed with complement modulation, and it wasn't clear whether modifying the complement pathway was going to work. Now we know that it does work, and it's providing significant hope to patients losing vision from GA. Now that the new drug is in our clinics, we have a very different patient education opportunity on our hands, considering that the treatment slows, but does not stop, progression. We asked experts in our field to share their thoughts on how they are approaching their care for a previously untreatable patient population and what pitfalls we must avoid.

— Allen C. Ho, MD, and Robert L. Avery, MD

DR. HO: HOW ARE YOU DISCUSSING THIS NEW THERAPEUTIC WITH YOUR PATIENTS?

Jeffrey S. Heier, MD: When patients with wet AMD presented 15 or 20 years ago, we did not have a treatment—then we had an explosion of anti-VEGF agents, and we were able to offer nothing short of a remarkable treatment that could control the disease and, in many patients, improve vision. But we also realized that dry AMD was a debilitating and unremitting disease that was continuing to affect patients' central vision. Thus, the development and approval of pegcetacoplan is an important step in our ability to control this disease.

I tell patients that we now have an FDA-approved therapy that has a modest benefit. It's a first step to slow the rate of GA progression. I make sure they understand that it doesn't stop it or reverse it; even with treatment, they will lose vision, just at a slower rate than if they did nothing.

For many patients, the earlier in the disease process that we diagnose their GA, before it involves the fovea, the more likely we can have a noticeable effect on their outcome.

DR. AVERY: WHAT ABOUT PATIENT SELECTION? FOR THIS DRUG, WILL WE BE APPLYING THE ART OF MEDICINE BECAUSE THE LABEL IS QUITE BROAD?

Eleonora M. Lad, MD, PhD: Although pegcetacoplan does not stop or reverse the disease, the effect is very meaningful because it preserves the cells in the retina that are responsible for vision for longer. In addition, we know that the protective effect of the drug increases with treatment duration. When recommending treatment for patients, I remember that it works best when treatment is initiated earlier in the disease process before the fovea is involved. I consider the visual status of the fellow eye, but I keep in mind that extrafoveal lesions benefit the most.

I have a full conversation with each patient about how nearly all medicines have side effects if they work. I also

AT A GLANCE

- The FDA approval of pegcetacoplan (Syfovre, Apellis Pharmaceuticals) for the treatment of geographic atrophy secondary to AMD provides patients with an option to slow the rate of progression.
- When recommending treatment, remember that pegcetacoplan works best when it is initiated earlier in the disease process before the fovea is involved.
- The authors are favoring every-other-month treatment for three reasons: efficacy (the difference between monthly and every-other-month dosing was only 3% at 24 months), treatment burden, and safety.



The approval of this first treatment for GA was important and historic. I truly look forward to more therapeutic options that will become available for GA and perhaps earlier dry AMD stages in the future.

- Eleonora M. Lad, MD, PhD

explain that one of the side effects is the potential conversion to wet AMD, for which we have excellent treatments. Otherwise, the drug was shown to be safe and well tolerated.

Patient selection will be a significant part of the art of medicine, and we must consider each patient's comorbidities, their ability to come in for frequent injections (whether monthly or every other month), and the status of the fellow eye.

Dr. Ho: The label is surprisingly broad with no restrictions for lesion size or location or whether the patient has concomitant wet AMD in an eye with GA. That may be a sweet spot for me—patients who have had chronic anti-VEGF injections to control wet AMD but are starting to decline from GA.

Dilsher Dhoot, MD: I applaud the FDA's decision to make this label broad. The studies were large and enrolled a very heterogeneous population. In fact, most patients in the OAKS and DERBY trials had foveal-involving lesions. The therapy isn't right for every patient, so it's important to have an informed discussion with patients. It's remarkable how many patients are aware of this drug already, and I've already had many asking if they are candidates for treatment.

When it comes to the decision to treat, the trials suggest patients who are treated early may have the greatest benefit. Patients who already have poor vision may not benefit from treatment, but I will still offer it to a wide variety of patients, similar to the inclusion and exclusion criteria used in the trials. In particular, I find that patients who have documented GA growth are great candidates for this drug.

Dr. Heier: I also plan to recommend treatment for patients with foveal-sparing GA. Still, I had a patient with center-involving GA come in today who asked why I didn't think he was a good candidate. He was aware that the drug slowed the progression of the disease, and he said it was important to have as small of a central lesion as possible. The patient brings up a good point. We've certainly seen patients



This is the first step in a very important path to hopefully get control of this disease. The goal of continued research is to ultimately stop progression, and with more innovative approaches, perhaps even reverse vision loss.

- Jeffrey S. Heier, MD

with bilateral disease with 20/400 lesions, but one is two disc areas and one is six disc areas, and the patient with two disc areas is noticeably better.

DR. HO: THE LABEL ALLOWS US TO TREAT EVERY 25 TO 60 DAYS. HOW ARE YOU DECIDING ON THE RIGHT TREATMENT INTERVAL?

Dr. Dhoot: With time, we'll have a better means of risk stratifying these patients, possibly with the help of artificial intelligence. But for now, I am favoring every-other-month dosing for three reasons. The first is efficacy. The difference between monthly and every-other-month dosing in the combined data set was only 3% at 24 months—a 17% reduction in lesion growth in the every-other-month group versus a 20% reduction in the monthly group.

The second is the treatment burden. The loss to follow-up was less in the every-other-month group—21% to 22% in the every-other-month versus 29% to 31% in the monthly group at 24 months. This is likely going to be greater in the real-world population, and offering a more palatable dosing scheme from the start is prudent.

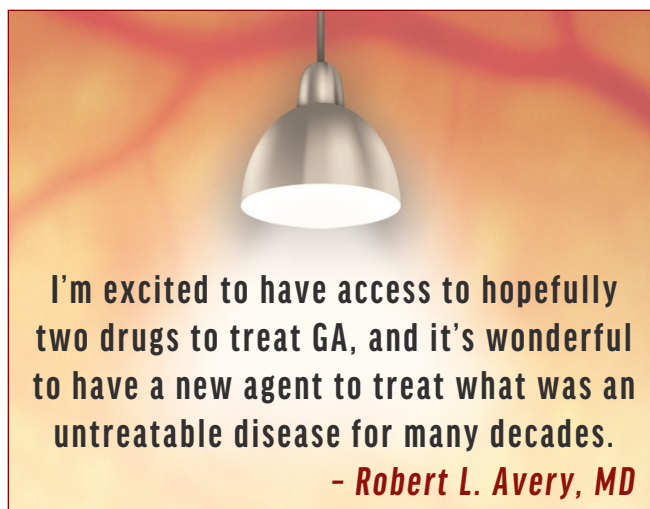
The third reason is safety. The rates of key adverse events, such as choroidal neovascularization (CNV) or ischemic optic neuropathy, were lower in the every-other-month dosing groups.

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That said, patients who are high risk with documented rapid GA growth that is parafoveal may opt for monthly or even every 6-week dosing. But most of my patients will likely begin with every-other-month treatment.

Dr. Lad: In the end, most of these decisions will be patient driven, and we must have thorough conversations about all these issues. We must also remember that these GA injections will add to our already large clinic volumes, and if a patient converts to wet AMD, we must decide how, and even if, we should give the two injections. Are we going to give the injections on the same day 30 minutes apart as in the trials, or should we give them on separate days depending on clinic flow and patient-physician preference? Patient preference will be a key factor in all these decisions.

There will be patients who will be very motivated to slow their disease progression, especially if they lost the other eye or if they really feel that the disease is encroaching on their central vision or impairing their peripheral vision. We will have a lot of chair time upfront to discuss these considerations and make a joint decision.

Dr. Heier: The main component that will drive my decision is safety because the efficacy is relatively close. There are clear benefits seen in the monthly over the every-other-month dosing, but the safety was also clearly better in the every-other-month group compared with the monthly group. The rate of CNV was roughly 12%, 7%, and 3% at 24 months for the monthly, every-other-month, and sham groups, respectively. The rates of ischemic optic neuropathy were clearly more prevalent in the monthly versus the every-other-month dosing groups. For most patients, the safety is going to drive that decision. Still, there are certainly some patients who will be extremely motivated to have as big an effect as possible and will want monthly dosing.

Dr. Avery: I completely agree, and in reference to safety, I have been focused on ischemic optic neuropathy; that was seen in seven patients in the monthly group, one patient in the every-other-month group, and no patients in the sham

group. Only three of the eight cases were severe, and these numbers may not hold as we progress to real-world experience. Still, this risk is pushing me to recommend every-other-month dosing, given that the efficacy is not that dissimilar.

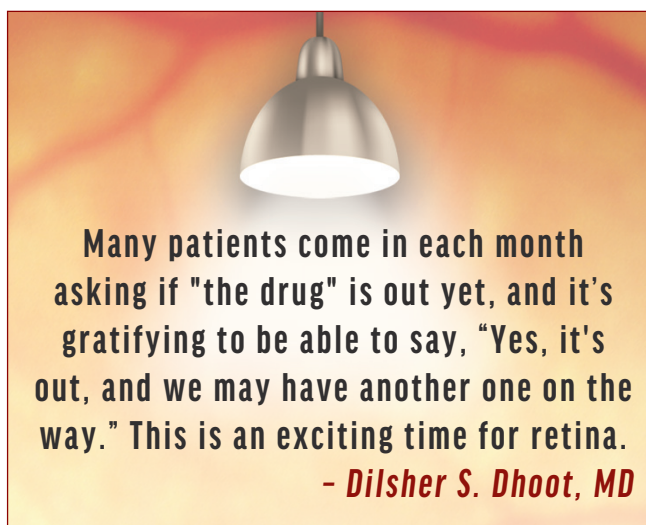
Safety is paramount, particularly because the ideal patients are often monocular. The most motivated patients have lost central vision in one eye from GA, and they are seeing well in the other eye. I want to protect the seeing eye, but minimize the risk of any sight-threatening complications.

Dr. Heier: It does appear as if those who developed ischemic optic neuropathy were largely patients with discs at risk, as well as other vasculopathic concerns. While there may be characteristics that you can look out for when treating these patients, the safety of the every-other-month dosing reduces this risk.

DR. AVERY: HOW ARE YOU GOING TO HANDLE WET AMD PATIENTS WHO ALSO HAVE GA? ARE YOU CONCERNED ABOUT BILLING TWO INJECTION CODES FOR THE SAME EYE WITHIN A 28-DAY WINDOW?

Dr. Dhoot: I'm quite concerned. There's a high chance that we will have rejected claims in the beginning, and we must be cautious. Unfortunately, many patients require treatment for both GA and CNV, and in the absence of anticipated payer issues, I would be comfortable injecting them on the same day. I would consider starting with the anti-VEGF injection because the volume is less, waiting 15 to 30 minutes between the injections, and then proceeding with the GA drug. Receiving reimbursement for two injection codes on the same day or within 28 days of one another may also be an issue. I'm hoping there will be guidance, and I'm optimistic that the billing will work itself out so that we can code and be paid for both the medications and the injection codes on the same day or within a 28-day window.

Dr. Ho: We have a data set that includes 12,000 injections, which is a large number of injections but not a large number



ARVO 2023 UPDATES

While OAKS and DERBY were not designed to evaluate visual function, Apellis released new post-hoc data at ARVO 2023 suggesting a modest visual benefit with pegcetacoplan (Syfovre) therapy: preservation of 5.6 letters at 24 months compared with sham. Results from patients' visual function questionnaire-25 showed a 4.1-point benefit in vision-related quality-of-life outcomes.¹

Iveric Bio also presented visual function findings from post-hoc analyses of the GATHER trial data. The researchers found that the reduced rate of vision loss in patients receiving therapy correlated

with reduced geographic atrophy (GA) growth—linking disease progression and worsening visual acuity. The company previously announced data suggesting a 56% risk reduction in the rate of persistent vision loss in patients with GA who were treated with 2 mg avacincaptad pegol compared with sham at 12 months.²

1. Apellis presents phase 3 functional analyses of SYFOVRE (pegcetacoplan injection) for geographic atrophy [press release]. Apellis Pharmaceuticals. April 23, 2023. Accessed April 26, 2023. bit.ly/3APgMcR

2. Iveric Bio announces new functional vision loss reduction data from avacincaptad pegol GATHER trials presented at ARVO annual meeting [press release]. Iveric Bio. April 23, 2023. Accessed April 26, 2023. bit.ly/3HtcuMg

of patients. It will be important for our community to be vigilant in monitoring for the safety issues that we may see when new products are introduced to the market.

We have not seen ischemic optic neuropathy with our anti-VEGF agents, which gave me pause, especially considering that these might be the vulnerable patients with only one good eye. We must monitor patients for safety issues and report our findings to organizations that provide systematic reporting, such as the American Society of Retina Specialists Research and Safety in Therapeutics Committee. We owe that to our patients.

But just like with anti-VEGF agents, which started with version 1.0, then moved to 2.0, and is now maybe at 3.0 with combination therapy, GA therapy will evolve. I'm happy that this is approved, and I hope that others will be as well. This allows the ecosystem to continue to invest in new treatments for this condition.

Dr. Avery: We've had major failures with prior agents, and I've been promising something to my patients for quite a long time. It's great to finally have something in the clinic that can help them. In the days of photodynamic therapy (PDT), we were just delaying the visual loss for patients with wet AMD. Innovation doesn't usually happen all at once, and PDT was just a steppingstone until we eventually discovered the anti-VEGF agents, which we have continued to improve over time. I believe that we'll make progress from this steppingstone for GA as well.

Dr. Dhoot: There's been some criticism regarding the vision benefit of this drug. In the trials, most patients had large foveal-involving lesions, approximately 8 mm in diameter on average. If we look at subsets of patients, I expect that it's easier to show vision benefit in smaller nonfoveal lesions. In these trials, they did show some vision benefit in terms of microperimetry data with a reduced number of scotomatous points in the 18- to 24-month period in the junctional zone of lesions. A second analysis presented at ARVO reports on vision benefit in patients with extrafoveal lesions (see *ARVO 2023 Updates*). I suspect over time we may see more benefit, but the size and location of the lesions may have blunted the

vision benefit in the overall population in these trials.

Dr. Lad: In addition, it is difficult to measure visual function in these elderly individuals; these are very noisy tests, microperimetry and BCVA included. These studies were not designed to evaluate function as a primary endpoint. To do that, Usha Chakravarthy, MD, PhD, CBE, and others have shown that you need to have a large dataset that includes small subfoveal lesions so that you have some area next to the fovea that you can monitor for treatment effect. This study was too short to pick up a functional change, although we might see it in the GALE extension study.

Still, we have a mixed population with more than 60% with large lesions—not the small lesions you need to measure function—and the rest are extrafoveal at different distances from the fovea. This type of study would require a different design where functional outcomes are primary.

DR. AVERY: WHAT ARE YOUR THOUGHTS ON IVERIC BIO'S DRUG, AVACINCAPTAD PEGOL, AND ITS STUDY THAT REPORTS LESS VISUAL LOSS OF THREE LINES OR GREATER WITH TREATMENT?

Dr. Heier: It's encouraging to see potential functional benefits from these agents. They are different studies, and it's hard to make cross study comparisons, although the Apellis study does have more than 400 patients that are nonfoveal as well. It's important to look at the safety and efficacy of each agent. All these opportunities to help discern which patients may benefit the most from these treatments will be important. Both Apellis and Iveric Bio are working to understand those outcomes and figure out how to use these agents best.

Dr. Ho: It's an incredibly important time for us and our patients. In addition to Iveric Bio, there are oral medications and gene and cell therapies under investigation for GA. We have a lot of shots on goal, but we need to start looking earlier in the course of dry AMD. ■

Editor's note: This manuscript has been edited from the original transcript for clarity and space purposes.

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