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GA Perspectives: An Unhappy Cataract Patient and a Patient Seeking Cataract Clearance

**Dr. Wykoff:**
Hi, I'm Charles Wycoff, Retina Specialist, Houston, Texas. Great to be here with you. Thanks for joining us. Here with a good friend and colleague, Yasha Modi, Uveitis and Retina Specialist from New York at NYU. And we're here to talk about a couple real-world geographic atrophy cases and sort of what we would both tell these patients and how we would manage these patients in the real world. And I'll tell you what I actually did with these patients also.

So, let's jump in. Just a little bit of sort of education at the beginning. What we care about most for our patients across retina is, of course, visual acuity. But what's fascinating, especially in geographic atrophy, is that we spend so much time looking at the anatomy. And there's not a perfect correlation. There's obviously a correlation between anatomy and function in GA, but it's not perfect. And the end of the day, we all talk to our patients, because what really matters is how are they functioning. And it's hard to take an asymptomatic patient and make them better. So, we're very hesitant to treat people, for example, with any form of AMD if they're asymptomatic.

Wet AMD is sort of an exception there, where many of us will initiate therapy in a wet AMD eye with a lesion that's close to the fovea, knowing what's the progression going to be. I think we're still trying to figure that out in geographic atrophy where these lesions absolutely progress. It's a major cause of blindness. But when to intervene, when not to intervene is still a very much an evolving question. And we have some really powerful clinical trial data to guide us with that, with both the avacincaptad and pegcetacoplan programs. And today we'll try to unpack a little bit of that data. Okay, let's jump in.

So, Yasha, here's our first patient. So, this is a 71-year-old male. So, on the younger side of GA here, still very high functioning in his life, he's pseudophakic OU and he shows up because he is unhappy with cataract surgery. We see that routinely, obviously, as a retina specialist, and that was in the right eye. In the left eye, he was happy with that. Now his function in the left eye is quite good. He's 20/25. That's why he's happy. But he's convinced that the cataract doctor somehow messed up his right eye. And he said he had problems before cataract surgery, but now after cataract surgery, it's not that it's a whole lot worse, it's just not a whole lot better. Like his neighbors and like everybody else around him, he's supposed to get better, right? But he didn't. So here on the OCT, you can see some loss here of the outer retinal structures on the B scan through the fovea in the right eye predominantly, and in the left eye, you see some early breakdown there. But then on the near-infrared images above that, in the right eye, you can see a relatively large area of geographic atrophy coming up towards the fovea on the inferior macula. On the right eye, it's more of an earlier picture there. Maybe not even any definitive cRORA at this point. But certainly, on the spectrum of AMD here in both eyes; 20/50 in the right eye, 20/25 in the left. Obviously at this point, there was no approved drug. Lots of clinical trials. I actually discussed clinical trials with this patient, and he said, 'No thanks. Not interested. Let's just follow this.' So, I reassured him that it wasn't the cataract surgeon's fault and that this was a disease inside the back of his eye.

So fast forward now. He comes back a couple of years later. And now he says, 'You know, I'm not so high functioning anymore. It's getting harder to read, particularly in the right eye, but now I'm noticing problems in the left eye.' Okay, so now we're in the realm of an FDA approved drug. This is about a month after pegcetacoplan was approved. And here's your fundus autofluorescence, right? The FAF signal of geographic atrophy in the right eye has essentially eclipsed fovea there inferiorly. And we'll look at the OCT in a second. And then in the right eye you can still see some preservation of the fovea. But more prominent obvious lesions of geographic atrophy

here also in the left eye.

**Dr. Modi:**
Yeah, a pretty considerable progression over a couple of years.

**Dr. Wykoff:**
Yeah, pretty rapid progression here. So now here's the cross-sectional scans, consistent with what we saw 2 years ago, the same pattern. And now you can see the right eye, the fovea has been lost. Those outer – that outer retinal structures have been lost. That's why the vision is decreased to 20/80, a meaningful decrease for the patient. And in the left eye, you can see that there is some foveal structures that are intact there. But there's some foveal structures that are lost.

So, one question for you, Yasha, would be is this – the right eye is obviously a foveal-involving geographic atrophy lesion. How do you qualify – how do you classify the lesion in the left eye? Is this foveal-involved? Or non foveal-involved?

**Dr. Modi:**
It's a great question, right? So, because in the clinical trials, it was based on autofluorescence diagnosis. But since then, we have the CAM classification. And it really sort of highlights the nuance of this. And here you have definitely ellipsoid zone loss. And that's one of the main fundamental reasons why this patient is struggling. So, even though the sort of fovea is spared, when you look at the near-infrared image, you can see that there's ellipsoid zone changes. And interestingly, when you look at who is likely to do well, individuals with better visual acuity are likely to have better sort of anatomic results with treatment. So, the right eye is sort of in big trouble at this point. And the left eye is one that, even with treatment, this is kind of a concerning feature.

**Dr. Wykoff:**
Yeah, all great points. This person was highly motivated. They were, you know, they did not want to lose more function. And of course, that's what our patients are focused on when they lose their foveal function; 'I don't want to lose more function, what can you do to treat me?' And the problem is our answer. If we're true to our discussion based on the phase 3 data is, we can't comment too much on function. Or we can comment, but we can say, look, there's no difference on your average visual function over the next 2 years. We need to focus on anatomy. And then we make this leap of faith that if we slow your progression, you're going to have preserved function, which I believe. I believe that leap of faith, but it still is a challenge and it's a disconnect in how we communicate with patients, because I cannot tell this patient, if we treat you, you have a higher probability of maintaining more vision than if we don't treat you.

**Dr. Modi:**
That's right, a challenge. And it's an all-in phenomenon, right? You have to – the hardest thing is not only is it going to be buy-in, but the hard – when this patient comes to you and they're 78 years old, and their vision is arguably worse than where it is right now, they still have to get treatment on a regimented basis. And so, understanding that, it's going to be really, really hard. And I think when we think about dropout in these clinical studies, that was not a trivial number of people. And so, I think that's the chair time that's going to be involved is to say, you're not going to see any better than where you are today. In reality, you're only going to see worse over time. But we believe that that's fundamentally going to be slowed relative to the natural history.

**Dr. Wykoff:**
Yeah, I have a very similar conversation. And after having that conversation with this patient, him taking home the literature and thinking about it, we've now initiated therapy in this patient bilaterally.

**Dr. Modi:**
How did you start that therapy? Did you start with injections in both eyes? Did you start with the right eye? What was sort of your – your sort of approach to a to get him into treatment?

**Dr. Wykoff:**
Yeah, I think it's very reasonable to start with one eye. But then again, some doctors start with both eyes, right? And if it's an FDA approved medication, I don't think that's unreasonable. In my own personal practice, I typically would choose to start with the worst eye first to make sure the eye – the human – the person tolerates the injection and the new medication well. So, in a case like this, I would start with the right eye. I started with the right eye in this case, treated him and then 1 month later, actually initiated therapy in both eyes when there was no adverse response.

**Dr. Modi:**
Right. And you and I have the exact same approach to this. Now, out of curiosity, are you treating them on a monthly basis? Or are you treating them on an every-other-month basis?

**Dr. Wykoff:**

My conversation with patients is every other month and monthly dosing, there's data to support both, they have a similar efficacy, but a little better safety profile with every-other-month dosing. And most patients with that simple discussion, sort of lean pretty quickly towards every-other-month dosing. Some patients do want that extra little bit of efficacy, and therefore we'll start with monthly, but most patients, ultimately, it's every other month.

**Dr. Modi:**
And your surveillance for inflammation and corneal neovascularization, when they come back is it that they're getting an OCT and an exam every time?

**Dr. Wykoff:**
OCT every time I see a patient, even if they come in for an adverse event like a subconj hemorrhage a week after an injection, I'm going to get an OCT on these patients every time I see them, looking for a lot of things. But one of those things is definitely an MNV.

And the point that you bring up is a great one. Because in the clinical trials, what was interesting is you need to make sure you're looking through the whole volume scan to see if there's any potential to conversion to wet AMD. Because it's sort of interesting; historically, when you're treating wet AMD with anti-VEGF injections, you know where to look on your scans and where the fluid is going to be. You sort of – you don't actually need to look through the whole volume scan, we of course, always should. And of course, we always do. But if you don't, you kind of know where to look. Whereas in this, the MNV could pop up anywhere theoretically on the volume scan. So, make sure you're comprehensive in looking through that.

**Dr. Modi:**
And you know what's really interesting is that if you look at the macular cube, what you can identify is that. If you just look at the volumetric map from one visit to the next, sometimes you may just see a little bit of area eccentrically thickened, and that should be your cue to maybe go over to that area and look at the cross-sectional scan there.

**Dr. Wykoff:**
The other thought was we do know that, you know, nonarteritic anterior ischemic optic neuropathy is probably a risk factor here to be aware of, typically with monthly dosing. Therefore, I typically tend to get a baseline retinal nerve fiber layer scan on all these patients.

**Dr. Modi:**
And then are you just sort of saying, I got it on this time, I'm going to repeat it every 6 months? Or what is your strategy?

**Dr. Wykoff:**
Every 6 to 12 months usually. Yeah, thanks. Great comments in the first case really appreciate that. Fascinating.

Second case is a 90-year-old, sort of a different stage of life here. First one was a 70-something, now we're in 90-something territory, and they're coming in for cataract clearance. Back up, of course, age is a major risk factor for AMD, and in particular, for geographic atrophy. Individuals older than 85 have a 10-fold higher prevalence of late AMD than those in the 70s to 74 range.

Okay, so here's your Optos images, again, 90-year-old woman here for cataract clearance in their left eye. Right eye already had a successful cataract surgery. Here's their fundus autofluorescence from 2020. So, we're 3 or 3+ years ago, you can see the zone of geographic atrophy there in the right eye superior to the fovea. And on the left eye, there's a little bit of a hazy view, again, secondary to that cataract. If you look at the OCT, again, hazy view on the near-infrared on the left consistent with the cataract and the B scan. But the fovea looks nice, intact in both eyes, 20/20 there in the right and 20/50 due to cataract. They have cataract surgery, they have no complaints. They're very happy actually in 2023. They're reading, they're functioning. And this is their fundus autofluorescence at this point. You can see the geographic atrophy on the right eye has expanded tremendously. Now they're still happy at this point. They're 20/20 in the right and the left eye, but they're noticing a little bit of changes. They're saying, 'Sometimes I lose words. Sometimes I lose my place on the page when I'm reading. I missed the exact domino that I'm supposed to play.' And you explain to them that this is likely due to the AMD.

So, in a context like this, Yasha, what's your feeling? Now there's a 92/93-year-old, but there's still high functioning, and they're happy with their vision, but they're noticing some problems.

**Dr. Modi:**
So, a few things. When you look, there's considerable progression in the right eye, even some in the left eye. And we know that geographic atrophy, it sort of tends to like, circle around the fovea. And it like, to get to the fovea can oftentimes take a long time. And so, you know, we're thinking about how do we extrapolate this out to 94, 95? How functioning are their – what's their medical history? We have a number of risk factors for progression, we have subretinal drusenoid deposits, perilesional hyper-autofluorescence, and then a history already showing progression. This is a tough case in terms of how do you factor in age into that decision-making? My guess is

I would probably have opted in this case to maybe observe. Maybe I want to see how they do over the next 6 months to a year. And then if there's some concern that this is migrating towards the foveal center rather than around the fovea, then I would consider initiating treatment.

**Dr. Wykoff:**
Very reasonable, and that was the exact discussion we had with a patient, with family. You know, look, these are the images, this is where you were a few years ago, it's clearly progressing, that alarms everyone. But then we sort of step back and say, look, this is over 2 or 3 years, I think observing here is very reasonable. The challenge is if we had an intervention that truly stopped progression, maybe that would change my opinion. But to know that it's going to slow the progression when this patient's already 92 or 93, high functioning, and one eye is clearly more advanced than the other. So in worst case scenario, if the right eye becomes center-involving, maybe you can initiate therapy at that point in the left eye. And I feel a little frustrated having to summarize the case in that way, because I would love to say, yeah, let's initiate therapy in both eyes.

**Dr. Modi:**
That's right.

**Dr. Wykoff:**
Let's slow this down. But it's a challenge. And it's always a balance in discussion with patients. And if this person were in their 70s actually, I would actually probably encourage a little more strongly thinking about initiating therapy in both eyes.

**Dr. Modi:**
Right. And you know, one of the things that I think clinicians are really bad at is sort of saying, what's the patient benefit? And what's the societal benefit? Right? You know, what's the cost to save vision? And is it worth it in somebody who's 94 or 95 versus 75? And it's a really hard conversation to have, right? We can't play that card. But fundamentally, we're kind of asked to do so in these cases. And it makes it really hard because now we're kind of imparting our own judgment on these cases. And I think that's how maybe you and I may get to a different answer. And I think it's going to be really, really difficult to know how to treat. There's no right or wrong answer in these cases.

**Dr. Wykoff:**
You bring up a great point. I think education of the patient and of their entire care delivery group, their family, is super important. So, I give handouts, I educate. I almost never initiate therapy for geographic atrophy the first time I'm seeing a patient; this is just not an emergency. It's worth patients understanding and all the people around them understanding before we initiate therapy, because you made a great point. This is sort of long-term therapy. If you stop dosing, we've learned from the pegcetacoplan data that you regress to the same trajectory of growth. So, you need to continue that therapy to maintain benefit long term.

**Dr. Modi:**
That sort of brings me actually to a question I wanted to ask you because I know you've had quite a bit of experience with pegcetacoplan. What's your strategy for those patients who may have missed a visit? So, is it something where, if they miss one or two visits, do we say this is game over and not worth it? Or how do you address those problems?

**Dr. Wykoff:**
No, in my experience, I've treated many patients at this stage. I think that incompliance is a challenge for all of the diseases that we manage. But I think of it actually very similar to wet AMD from a lost-to-care perspective. If people are lost to follow-up for whatever reason, you do the best you can moving forward. You know, life you can only move – you can only live moving forward. You can learn from the past, but you can't change the past. So, if a patient misses a few visits, which is certainly going to happen in this population, I think, then you can always revisit, do we want to continue treating this, but if the answer is yes, then it wouldn't change my pattern.

**Dr. Modi:**
Right. Okay.

**Dr. Wykoff:**
Have you thought about it differently?

**Dr. Modi:**
You know, I haven't had enough patients with long-term follow-up. But I do say that there is no benefit if we're missing visits. So, if we are getting committed to this, we need to be 100% committed. So, if you miss one visit because something happened or you got sick, we really try to want to get you back in here the next week. And that's hard for clinic volume and flow. But, you know, that's also about re-educating our front desk staff and, you know, our technicians and sort of saying, how do we get these patients through in a fast-track kind of method without missing some of the complications associated with it?

**Dr. Wykoff:**
We don't really know the pharmacokinetic or pharmacodynamic sort of implications of that. Right? We have 1-month, 2-month intervals, very robust data with pegcetacoplan. But we don't have 6-week interval, you know, and we don't have 10-week interval. We don't actually know that if you go beyond 2 months occasionally, 3 months, it's going to make any difference. It might, and it's likely that it would decrease the growth rate a little bit but, you know, we know if you stop over the next 6 months, it goes back to baseline growth. I think an occasional miss here or there, I don't think we should take that as a loss, and we should keep doing the best we can.

**Dr. Modi:**
Yeah. All excellent points.

**Dr. Wykoff:**
Thanks for all your comments. Greatly appreciated going through this case with you. Hope everyone out there learned something along the way. Thanks.