Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/ga-perspectives-surgeon-with-blind-spots/16480/

Released: 12/20/2023
Valid until: 12/20/2024
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

GA Perspectives: Surgeon With Blind Spots

Dr. Wykoff:
Hi. I'm Charles Wykoff, Retina Specialist from Houston, Texas. It's an absolute privilege to be here with a good friend and colleague, Yasha Modi, from New York. He's at NYU, he's a Retina and Uveitis Specialist, and we're here today to talk about retinal cases, specifically today looking at geographic atrophy. And before we get into a fascinating case of Yasha's, he's going to walk us through some of the criteria around the recent phase 2 and phase 3 trials in geographic atrophy.

Dr. Modi:
Alright, well, thank you so much, Dr. Wykoff. It's always a pleasure doing these programs with you, and, you know, when we think about the inclusion criteria, there were some subtle differences between those who are enrolled in DERBY and OAKS, and those who are enrolled in GATHER1 and GATHER2. Their similarities is that they all had similar size of geographic atrophy, between 2.5 and 17.5 mm^2 of GA. They also had to have perilesional hyper-autofluorescence – basically, they all had to have an autofluorescent image, and it all had to be sort of hyper-autofluorescent on the margin, and if they were a multifocal, they had to at least have lesions greater than 1.25 mm^2. So – and we know multifocal lesions are more likely to progress faster. And interestingly, they basically if they had geographic atrophy secondary to any other condition, such as Stargardt's, they would have otherwise been excluded, but it's a little unclear as to how we would exclude them outside of a clinical examination and a reading center. And that's kind of one of the cases that I'd like to discuss today.

Now, if you move on to GATHER1 and GATHER2, basically they had to have essentially near center point-involving geographic atrophy – had to be within 1500 microns of the center, so the location was much more specific in GATHER1 and GATHER2, but the lesion size was effectively the same.

So, I'd like to go into an interesting case. But before we do that, it's only pertinent to talk about a very recent update that it was sort of released by the ReST committee, and this was a update on pegcetacoplan, identifying within 7 to 13 days after injection, a small number of patients who had mild to moderate inflammation, but there were cases of severe intraocular inflammation and retinal vasculitis, specifically of the occlusive type, was identified in 6 of these patients. Now what's interesting is that this all occurred after the first injection, so kind of unlike the, sort of, brolucizumab story, it's not like they're occurring after multiple injections, and from – to the best of our understanding, we can identify that probably there have been about 60,000 units sold, which yields an incidence of severe occlusive vasculitis in about 1 in 10,000 patients. And so that's going to be kind of pertinent as we start thinking about the risk-benefits analysis as we are starting new patients on these treatments, and this is an evolving topic. This is something that we're certainly going to have to kind of all grapple with as retina specialists going forward.

But, I'd like to start with a case. This is a patient of mine. I first met him in November of 2021. He is 72 years old at that time. He's a practicing surgeon who presents with blind spots in his vision. His vision is otherwise excellent, it's 20/20 minus in the right eye, 20/25 in the left eye. And you sort of see that pattern where you have ellipsoid zone preservation, kind of in the center, and there is extensive areas of atrophy in the sort of paracentral regions. And I want to show you a couple of the horizontal slices. Now, I love near-infrared imaging, because I think it highlights the extent of geographic atrophy with some degree of clarity. In the right eye, at the top image there, you can see essentially an area of hyper-fluorescence – or, so basically, hyperreflectivity I should say, excuse me. And that is

corresponding to a choroidal nevus. So that sort of hides a little bit of the extent of geographic atrophy, but in the bottom image you can see very clearly geographic atrophy surrounding the fovea. And there's also an outer retinal tubulation on the nasal side, and that becomes important and we'll talk about that. So, here's the fundus photo. You can clearly see the choroidal nevus, and in the left eye you can see, essentially, the geographic atrophy, but notably we don't see really drusen, per se. And that's going to be kind of an important conversation as to when we think about how do we manage these patients. How do we define these patients with extensive geographic atrophy? And here's sort of the autofluorescent patterns. So, the area in the right eye, you can see a clear area of GA loss of geographic atrophy, superior to the fovea, and then geographic area atrophy surrounding the fovea in the left eye, with much more extensive, hyper-autofluorescence involvement in the left eye.

Dr. Wykoff:
Let me pause you there.

Dr. Modi:
Yeah.

Dr. Wykoff:
When you look at these images, do you think this would meet criteria, on this particular fundus autofluorescent image, of the hyper-autofluorescence around the area of atrophy? I always kind of, you know, wonder what that means. Like, obviously as you're pointing out, this isn't a slam dunk AMD case.

Dr. Modi:
Absolutely. Yep.

Dr. Wykoff:
A lot of it looks like that, but there are some, you know, unique features, star pattern pigment, the linear streaks there on the right eye, in particular, that may not be AMD, but there is some hyper-autofluorescence around the lesions. Would this qualify?

Dr. Modi:
Well, I think by the reading center definition of hyper-autofluorescence, it probably would qualify. It qualifies by size, it qualifies by location, and it qualifies by the extent of hyper-autofluorescence. Now, as retina specialists, you're sitting there like, is he missing some sort of pattern dystrophy? Is he missing an inherited retinal degeneration? What else is going on in this case? And so, we did investigate that to some degree, and you know, I sort of thought very similar to you, you know, there is this absence of drusen. But as we naturally get older and GA progresses, we lose those natural drusen burden, and it becomes sometimes a little bit harder to differentiate what's age-related macular degeneration from something that's inherited. But remember, he's only 72 years old at this time. We also have extensive geographic atrophy, so of course we're primed to ask about a medication history. He's not on any specific medications. He's not on pentosan polysulfate. And I did end up doing genetic testing, because like you, I was worried. Could I be missing something? Could I be missing an inherited retinal degeneration? And quite frankly, the retina specialist that I like to give credit to is Danny Mammo, who kind of pointed this out to me, is that possibly we can have these GA cases, would have otherwise been enrolled, but maybe not necessarily classified as the classical form of age-related macular degeneration. And so, my working diagnosis at this point, after that workup, extensive geographic atrophy, possibly advanced – atrophic AMD with extra foveal involvement. I think these patients, based on the criteria in our conversation, were likely enrolled, and so they would have fulfilled the inclusion criteria, and probably been thrown into the more classical forms of age-related macular degeneration. And as you follow this patient over time, I'm going to just show some change analysis, and you can see that overall, as we go through every 6 months, the changes are not drastic. And so, I want to show you here, here's 2021 to 2023, and there is some loss of the ellipsoid zone. We're talking microns of loss, but here he's only 74 years old. So, if we extrapolate this over decades, where does he end up? How much longer does he have as a operating surgeon, before we have to go and throw in the towel and say that's not a viable option?

Dr. Wykoff:
The other thing that comes to my mind when you show me these images is just the huge unmet need in our field for a software system that allows us to graph this. We need an automated system that actually measures geographic atrophy over time. Because I agree with you – those images that showed me, it's clearly getting worse, but a little bit subjective here. It's a little bit of, you know, qualitative. It'd be great if we could quantify that, and learn what those trajectories are, looking back at our patients over time.

Dr. Modi:
That's right. That's right. And you know, in this particular case, there are – fortunately, there are some algorithms, ZEISS has a RPE analysis that can basically measure area, which can be remarkably helpful. I didn't show that here. This is actually Heidelberg imaging, but I think there's a lot of quantitative software that we can use. And then, there's also a directionality to the fovea component, like it is migrating? Or do we have ellipsoid zone loss closer to the fovea? Because not only is area important, but progression to the fovea is

arguably sometimes the most important thing.

And what we also know is that even though those slight ellipsoid zone loss, outer retinal tubulations have been associated with slower geographic atrophy progression. And so, it's really – like to your point, I think this is one of those gray cases. We're not really 100% certain on the true diagnosis here, and – but this is somebody who has extensive GA, and our options are do nothing versus something, where we only have one FDA-approved drug at the moment that can potentially slow this progression. And so, you know, does a atypical macular exam alter your decision-making in deciding on complement inhibition? What would be your conversation with the surgeon in your community.

Dr. Wykoff:
I completely agree with all the points that you described. It's nice to have historical data. For example, if I was seeing this patient the first time, as a 72-year-old complaining of symptoms, I'd be a little hesitant to call this definitely AMD-related, and I'd want to see them – some change over time. You're in a position that's nice, where you have that historical data showing progression, so that's useful. Because there are certainly some atypical cases that may not progress, and what we don't want to do in the real world is find a bunch of people with static areas of atrophy that are getting treated when they're not going to get any benefit from that. So, it's nice, and it – especially in atypical case, to be able to show historical progression, I think, to lead us towards the right recommendations for patients.

And then, secondly, I think you did the appropriate thing, which was a genetic workup. Of course, the problem there is it's not 100% sensitive, so we may have missed something in the genetic workup, that could still be an inherited retinal disease. I think at that point, where you're not sure, but it's a high probability of being an atypical AMD case, giving the patient the information, being fully transparent with the risks, the benefits. You know, one of the biggest challenges here is we all agree that there's a benefit from anatomic perspective, and slowing change that we can measure on the fundus autofluorescence and OCT. Where does that translate into a functional benefit? The surgeon's obviously acutely aware of his vision, and he wants to maintain that, and the challenge is that we don't have great data to guide him. We have a little bit of, you know, post hoc data from both of the programs, showing that we may be able to preserve vision, and slow the really severe vision loss cases. But we need more data to support that.

Dr. Modi:
Absolutely.

Dr. Wykoff:
Was he asking about the vision benefit of treatment?

Dr. Modi:
So he was, and he actually was well-informed. You know, the beauty of working in Manhattan is that he actually had read DERBY and OAKS, and he had come to me asking me whether or not he would be a good candidate for pegcetacoplan.

And, you know, one of the interesting features – we talked about the inclusion and exclusion criteria, and you hit on something that is, what is I think the huge deficits in those studies, is that there was no look back to see what their rate of progression beforehand. We're looking at one cross-sectional moment in time, and so then the question is, are these patients going to progress quite rapidly? Are they going to be somewhere in the middle? Or are they going to be slow progressors? And now I think there are, sort of, like post hoc analyses that are starting to look at these questions, but it certainly would be helpful to know that data, a priority.

Dr. Wykoff:
Yeah. Great point. It's amazing as I'm involved with, you know, looking at real-world cases outside of this case, it's amazing, because when you graph dozens, hundreds of cases, you get these nice trajectories of change over time, in a, you know, in an observational population. But each individual patient can vary quite a bit, and they may be different from a 3- or 6-month segment, and the next 6-month segment. So, while we want to look back historically, I think that data's really important, as you point out, it's not always translatable to the next 6 months, which is really frustrating to see.

Dr. Modi:
That's right, because as we have greater multi-focality and greater lesion size, the rate of atrophy picks up over time, so it's not like you can graph it on a linear scale, and I think that's kind of what these AI algorithms are trying to evaluate over time, is how do you take into account that differential rate of progression? But I think we're kind of a long ways away from that, but today in 2023, how do we make a decision for this patient? And so, would you just say, if this person showed up in your clinic, would you start treating this patient?

Dr. Wykoff:
Good question. I would definitely – I'm glad that they're informed. Glad they've actually read the papers, and I would talk to them about the risk/benefit ratio here, and that the challenge is that they're going to be highly motivated, because they're obviously a hard worker. They're in their 70s and still an active surgeon, so you want to give them the benefit of treatment when there is only one option. But if I

did initiate, I would certainly initiate probably in their worse eye. I would do one eye at a time, and I would see if they tolerated the first eye well, and then think about initiating the second eye later. I mean, the challenge is you're not going to have a short-term biomarker, to see if it's, quote unquote, working. And all you could potentially have is changing the historical trajectory, and we already said that that's fraught with challenges. So, it's difficult, and I think your last one here is a good one, and I'm curious what his perspectives were, because this is an informed surgeon that used to giving risk/benefit discussions with his patients, presumably.

Dr. Modi:
Right.

Dr. Wykoff:
So now, for his perspective, knowing that there's a 1 in 10,000 chance, or somewhere in that ball park, let's just hypothetically say, of a bad outcome, you know, whether it's vasculitis or inflammation that causes vision loss, with an occlusive vasculitis. Would – did that change his – for the –

Dr. Modi:
He actually does not know about the ReST committee report yet, which came out last week.

Dr. Wykoff:
Yeah.

Dr. Modi:
And so, we have not had a conversation about that, so I think that certainly changes the algorithm. But, when you think about it, to the best of the ReST committee's, sort of, thought process, the incidence is about 1 in 10,000. What's missing in that report is the severity of vision loss, and the severity of inflammation, which I think remains unknown at this moment in time to the average retina physician. And so, I think we need to kind of understand that a little bit more. When we think about rates of endophthalmitis, we're typically quoting rates of 1 in 2,000, into 1 in 4,000.

And what you and I both know from endophthalmitis is some people can do really well, some people can do very, very poorly. We don't frequently make a decision to treat or not treat, based on that risk. But here, now, you have a drug-specific risk that probably results in some overactive immune response in the patient. That's a different story, and I think it's really hard, but unlike the brolucizumab story, in this case, this is a first-in-class. We don't have any other alternatives. And I think weighing all of those factors is going to be a really hard thing, and I think that's going to be a moving target for a lot of retina specialists over the next few months.

Dr. Wykoff:
Great comments, great case. Thanks for the discussion. Really enlightening and a lot to think about. Great to have a new drug in the space, but a lot to unpack.

Dr. Modi:
Of course.

Dr. Wykoff:
Thank you.

Dr. Modi:
Yep.