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Making the Case for Dual Ang-2 VEGF-A Inhibition: Durability and Drying

Announcer:
Welcome to CME on ReachMD. This activity, titled “Making the Case for Dual Ang-2 VEGF-A Inhibition: Durability and Drying” is provided by Prova Education.

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Dr. Regillo:
New treatment modalities are now available for our patients with neovascular age-related macular degeneration [nAMD] and diabetic macular edema [DME]. One agent is unique by targeting both VEGF-A and angiopoietin-2, or Ang-2, but what are the biomarkers that indicate dual targeting is helping to reduce vascular leakage and suppress neovascularization?

This is CME on ReachMD, and I'm Dr. Carl Regillo.

Dr. Lim:
Hi, I'm Jennifer Lim.

Dr. Regillo:
So when it comes to visual outcomes, fluid resolution is important to us as retina specialists. Let's first consider drying in neovascular AMD and DME. Certainly, the presence or absence or even degree of fluid guides treatment decision-making. And we want treatments to keep the macula dry for the longest period of time. Jenny, what are your thoughts?

Dr. Lim:
Yeah, I think it's really important, Carl, to get that retina dry as soon as possible and to keep it dry in the long term because we don't want the retina to stretch and then decrease and stretch and decrease because that causes undue stress on the internal retinal elements which can ultimately result in decreased vision or a lack of response to vision, despite the fact that the retina is being thinned.

Dr. Regillo:
I certainly agree. We know that severity matters. We know the chronicity matters, but we also know that fluctuation matters. So as you said, get the macular dry, as complete as possible, and keep it dry for as long as possible.

We've seen earlier and faster resolution in both neovascular AMD and DME to some degree with the new so-called second-generation intravitreal biologics; faricimab is the dual-acting antibody. Preclinical vascular data in leakage strongly suggests the pathologic role for both angiopoietin-2 and VEGF-A; we know that. In fact, Ang-2 is upregulated in these disease states. Earlier fluid resolution in clinical trials has been demonstrated. For example, the first absence of intraretinal and subretinal fluid occurs sooner with faricimab in both neovascular AMD and DME in phase 3 studies, or complete drying overall that is achieved faster and with less treatment. We're also seeing significantly greater CST [central subfield thickness] reductions, on average, both early on and over time with faricimab in the DME studies, the phase 3 trials, and that's compared to standard-dose aflibercept. Lastly, there's also less fluorescein angiographic macular leakage with faricimab in DME in the matched initial-dosing phase of the phase 3 DME studies.

What about aflibercept 8 mg? That's the higher dose of the original 2-mg aflibercept anti-VEGF fusion protein. Well, it was the PULSAR

neovascular AMD and the PHOTON DME studies that showed good extended durability in both of these disease states over 1 to 2 years. Less consistent benefits, however, with regards to CST reductions overall compared to 2-mg aflibercept, except there has been some analyses that point to maybe median time to fluid-free center faster in neovascular AMD and maybe longer drying in DME.

Jenny, what are the clinical data about faricimab to treat pigment epithelial detachments, or PEDs?

Dr. Lim:
Well as you know, Carl, PEDs are very common in neovascular AMD. This was true as well in the TENAYA and LUCERNE trials for neovascular AMD using faricimab as compared to aflibercept 2 mg. And in fact, in the study, about 80% of eyes did have a neovascular component due to the PED. And the PED predominantly was a fibrovascular PED, although about 20% were predominantly serous PEDs. And when we looked at the OCT [optical coherence tomography] change in the maximum height of the PED, we saw greater reductions for the eyes treated with faricimab than the eyes treated with 2 mg aflibercept.

And we broke this down further looking at the types of the PED, fibrovascular PED and then predominantly serous PED. And so for the predominantly fibrovascular PED, there wasn't a statistically significant difference in the maximum PED difference between the 2 drugs. However, when we looked at the serous PED, there was a significant difference. And basically, at baseline, about 20% of the eyes in faricimab, as well as 20% of the eyes treated with aflibercept, had a predominately serous PED at baseline. At the end of the head-to-head phase when both drugs were given at the same interval in the same number, fewer eyes had a predominately serous PED remaining. It was basically 3.9% for the faricimab-treated eyes, down from 20%, essentially. And for the aflibercept eyes, it was about 12%, down from approximately 20%. So you see there was a greater reduction for the eyes that received faricimab than for aflibercept. And this is quite heartening because, as we know, it's really hard to get PEDs to flatten, and it's nice to know that this new bispecific antibody can result in greater reductions in the fluid components in the PED itself.

Dr. Regillo:
Yeah, this is impressive because, as you said, serous PEDs are traditionally quite resistant to our anti-VEGF therapies. And when we reduce PEDs, we do tend to see vision improvement, so it does matter. If we can get rid of them, all the better.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Carl Regillo, and here with me today is Dr. Jennifer Lim. Today, we're discussing vascular leakage as a biomarker of dual VEGF and Ang-2 targeting.

Jenny, can you show us a case of a patient with a PED that's been treated with faricimab?

Dr. Lim:
My patient that I'm going to share with you, Carl, is an 85-year-old woman who has a disciform scar in her right eye from AMD and also had PVR [proliferative vitreoretinopathy] retinal detachment. And her previously good left eye developed neovascular AMD. And we see in July of 2023 that her vision dropped from her baseline of 20/50 down to 20/300. And there were significant components of intraretinal fluid, subretinal fluid, SHRM [subretinal hyperreflective material], and of course the predominately serous PED shown here, and other smaller PEDs off to the side. I went ahead and gave her a faricimab injection. And you see after one faricimab, her vision has now improved to 20/80 and holding to 20/70 in this left eye. And the serous PED is predominantly gone. And you can see that the intraretinal fluid, the subretinal fluid, and the SHRM is almost all gone as well.

After her second faricimab, her vision is 20/100, and there's further resolution of the intraretinal hyperreflective foci, the fluid compartments, and further reductions in the adjacent PED components. So this lady went under a treat-and-extend treatment for faricimab. And eventually, after 4 faricimabs, you see that her visual acuity is 20/60, so she's back to baseline in this left eye, and essentially, there are no PED components, no intraretinal fluid, no subretinal fluid, and marked resolution of the SHRM and the intraretinal hyperreflective foci. And I will add, Carl, that at this point she is on q4-month therapy. So as I was going along, I was treating her and extending the interval by 1-month intervals, as was done in the TENAYA and LUCERNE clinical trials.

So what do you think, Carl, after seeing this?

Dr. Regillo:
Well, at first, I was going to say you had a homerun because very impressive, very quick reduction in all signs of exudation, including the PED. But actually, I just changed it to a grand slam, because you got not only a great anatomic benefit very quickly, you then had a very durable effect. And so the patient benefited, and the stakes are high, of course; this was the patient's good eye. And, boy, you got a phenomenal vision outcome here and there's a good chance you'll be able to keep it good. And you're able to do that with fairly infrequent treatment. So that's really impressive.

Dr. Lim:
And I do want to add as well, Carl, that in the studies, we didn't see any excess amount of RPE [retinal pigment epithelial] tears. And

this patient, too, did not have a pigment epithelial detachment tear with the treatment, which was kind of a nice added bonus.

Dr. Regillo:
That's a good point you make, because in the past, sometimes we thought the agents that were, quote, stronger or better drying might put our patients at increased risk for RPE tears, which often decrease the vision and result in poor outcomes, but I don't think that's necessarily the case. And it doesn't seem to be the case, backed up by the data you just mentioned. So that's really, you know, a lot in one case in terms of demonstrating not only how well the agent works, but I think also tells us more about the potential dual-acting nature of this biologic.

You know, I've really enjoyed our discussion here. As we wrap up, Jenny, what's your one take-home message for our listeners?

Dr. Lim:
My take-home message would be consider using this bispecific antibody that targets not only VEGF but also Ang-2, because in situations such as pigment epithelial detachments with associated neovascular AMD, you really can get some really terrific results with reductions in all fluid compartments, improvements in vision, and fortunately, this can be done with relative safety.

Dr. Regillo:
And for DME patients too, right? They often can be very challenging and take a long time to resolve their signs of exudation, and we know that matters too. Again chronicity, especially in DME, can result in worse vision outcomes if you can't get the macula dry quickly. So I agree. When the situation starts with a lot of exudation and a lot of vision loss, it makes sense to turn to perhaps the best drying drug we have first. And if you're starting with other drugs or have patients that have an incomplete response to older agents, it makes sense to think about switching sooner to get a better outcome. And I do believe better drying for a longer time frame will help us to get better real-world vision outcomes with these new drugs.

Dr. Lim:
I'd like to add that in the real-world studies that have been done, they are showing the same drying effect in terms of the fluid compartments for patients who are difficult to treat. And then also patients who are treatment naïve, they are getting similar results that we've seen in the clinical trials, lending more evidence that this drug is a better drying agent.

Dr. Regillo:
That's another good point because in the real world, sometimes we have even more challenging patients, patients that wouldn't have necessarily made it into a clinical trial because their disease severity was so much greater than what could have been allowed in the inclusion criteria. So that's another good point. The fact that real world is mirroring the types of better drying and better durability, we were able to demonstrate in these prospective clinical trials.

You know, that's all the time we have today. And thank you, Jenny, for joining me. It was really a pleasure speaking with you.

Dr. Lim:
Thank you, Carl. My pleasure as well.

Announcer:
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