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The Future Is Now: New Data for nAMD and DME in Vascular Integrity

Announcer:
Welcome to CME on ReachMD. This activity, entitled “The Future Is Now: New Data for nAMD and DME in Vascular Integrity” is provided by Prova Education.

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Dr. Do:
Multiple second-generation medicines are emerging for the treatment of neovascular age-related macular degeneration [AMD] and diabetic macular edema [DME]. But how do we use these new agents in clinical practice, and what are the pathogenic drivers of these diseases?

This is CME on ReachMD. I’m Dr. Diana Do, and joining me today is my friend and colleague, Dr. Jack Wells. Welcome to the program, Jack.

Dr. Wells:
It’s a pleasure to be here, and I’m looking forward to talking to you. So let’s start our discussion by going straight to the question you just asked about these new medicines. We know that our currently available agents – aflibercept, ranibizumab, bevacizumab, brolucizumab – all target VEGF-A, and then we now have this new approved drug, faricimab, that targets VEGF-A and angiopoietin-2. We know that VEGF-A is a very potent driver of angiogenesis and vascular permeability, but what’s the role of Ang-2 and its receptor, Tie2, in these retinal diseases that we treat every day?

Dr. Do:
We know that retinal vascular diseases are very complex, and VEGF-A is not the only driver of these diseases. The angiopoietin pathway actually is important because it maintains vascular stability and homeostasis under normal physiologic conditions. When the retina is diseased, there is up-regulation of angiopoietin-2. Too much Ang-2 promotes vascular instability in these diseased states. And therefore, it would be important and helpful to potentially block Ang-2. Faricimab is the first bispecific molecule that inhibits both VEGF-A and angiopoietin-2. We can learn more about how Ang-2 blockade is important by looking at this animated video.

[VIDEO PLAYS: Therapies targeting VEGF-A have become the gold standard of care to combat choroidal and retinal neovascularization and leakage. A new generation of strategies is emerging with the goal of better drying and greater durability. Brolucizumab is a single-chain antibody fragment binding VEGF-A to block angiogenic signaling. Faricimab is a bi-specific antibody targeting both VEGF-A and angiopoietin-2 or Ang-2. In diseased vessels, Ang-2 and VEGF synergistically drive vascular instability. Ang-2 competitively binds Tie-2 receptors on endothelial cells to prevent quiescence driven by Ang-1. Binding of Ang-2 by faricimab enables Ang-1/Tie-2 signaling. The combined inhibition of Ang-2 and VEGF-A suppresses pathologic angiogenesis and improves vessel stability.]

Dr. Do:
Jack, how effective is faricimab in neovascular AMD and diabetic macular edema? Can you briefly review the phase 3 clinical trials?

Dr. Wells:
Certainly. So this has been a very exciting past month or two because we've had presentations of the phase 3 faricimab data for neovascular AMD in TENAYA and LUCERNE and for DME in YOSEMITE and RHINE. So in the AMD studies there were 665 eyes, if you pool the studies, that were treated with either faricimab or compared to aflibercept for wet AMD. And what we saw at the 1-year primary endpoint was that the visual outcomes were similar. There was about 6 letters gained in both groups, and the CST [central subfield thickness] reductions were also similar with faricimab to aflibercept.

But the exciting thing was that there was a significant durability signal. At 1 year 45% of eyes in the faricimab group were on a Q16-week dosing interval, and another 33% of eyes were on a Q12-week dosing interval, so 78% of eyes were on Q12 weeks or longer, which is certainly an impressive interval for the treatment of wet AMD. In the phase 3 DME trials, YOSEMITE and RHINE, these were large DME studies – the largest ever, I believe, with almost 1,900 patients enrolled. And these studies included 2 faricimab arms. One arm gave faricimab on a fixed 8-week dosing schedule after a loading period of 6 doses, and then the other arm was called the personalized treatment interval [PTI] arm, which gave 4 loading doses of faricimab and then additional treatment was given according to whether the eye was stable, worsening, or improving. Intervals could be extended as long as 16 weeks, and again, these faricimab arms were compared to aflibercept. And what we saw at the 1-year primary endpoint was that the visual and anatomic outcomes were noninferior to aflibercept in both faricimab arms.

But I really want to focus on the PTI arm, which was essentially a treat-and-extend arm, and at 1 year just over 50% of eyes in the PTI arm were on a 16-week dosing interval, and another 20% were on a 12-week dosing interval. So you had 70% of eyes at 1 year on a 12-or-longer dosing interval. So the recent presentation of the 2-year results of these studies was highly anticipated because we wanted to see if this durability signal was sustained through 2 years. And indeed, it was not only sustained, it was increased. At the 2-year timepoint, 60%-65% of the faricimab-treated eyes were on a Q16-week dosing, and another 15%, roughly, were on Q12-week dosing, so it was 80% of eyes were able to go 12 weeks or longer between their dosing. And again, this was without any loss of efficacy in terms of vision or central subfield thickness reduction.

We also saw some new data from the brolucizumab studies, KITE and KESTREL, looking at a treatment of DME, and it had good efficacy, but again, the safety concerns with brolucizumab are likely to limit its use. Fortunately, with faricimab, there were no safety concern. There were no increased rates of intraocular inflammation, and there were no cases of retinitis or occlusive vasculitis with faricimab, so that was very encouraging to see that.

So if you want more information on the efficacy of these agents, please visit EyeHealthAcademy.org.

Dr. Do:
For those just tuning in, this is CME on ReachMD. I'm Dr. Diana Do, and today I'm joined by my friend and colleague, Dr. Jack Wells. We're discussing second-generation medicines for the treatment of both neovascular age-related macular degeneration and diabetic macular edema. We're looking at the new mechanisms of action and how these translate into clinical outcomes.

Jack, thank you for that review of faricimab's clinical data. How should we think about using faricimab compared to aflibercept or ranibizumab in eyes with neovascular age-related macular degeneration?

Dr. Wells:
Well, Diana, you know as well as I do that one of the difficult things about treating patients with wet macular degeneration is that it's a chronic disease, and patients frequently need to be treated on a monthly or nearly monthly basis to keep their disease stable and keep their vision stable. The exciting thing about faricimab is this durability signal that we've seen in these studies. And so I frequently treat patients with aflibercept or ranibizumab, but those patients that are treated with those medicines that are requiring monthly therapy, I'm certainly going to look to switching them to faricimab to see if we can get that extended treatment interval. As I gain experience with faricimab in that fashion, I'll certainly be continuing to use aflibercept or ranibizumab, but I will start to hopefully use faricimab in my treatment-naïve patients as well.

Dr. Do:
I agree with you completely. I think there certainly is a role for faricimab with its new compelling data, but I think the safety records of aflibercept and certainly ranibizumab also are excellent, and certainly many patients continue to receive these therapies and do well, too.

Let's move on to diabetic macular edema. How will you use faricimab in patients with DME, Jack?

Dr. Wells:
So I think I'm probably more excited about the diabetic data, maybe because so much of my previous work has been in DME. So I think one of the interesting things about the 2-year data with faricimab in YOSEMITE and RHINE is that in the PTI arm, the mean number of

injections given in the second year was only 3, and we know from Protocol T that when you compared the available agents, that the mean number of injections given in the first year was 9 or 10, and it was 5 to 6 in the second year. So you're talking about cutting the treatment burden in the second year at least by half. We also know from Protocol T that chronic persistent diabetic macular edema is very common. It's up to 40%, 50% of eyes that after 1 year of treatment still have thickening, and you don't really see that. When you look at the OCT data with faricimab, you see there's a dramatic anatomic improvement in the first few months, and really, after 6 months, over 80% of eyes have what was defined in the study as absence of DME, meaning their central subfield thickness had fallen below the threshold. So I'm looking forward to taking my patients with chronic persistent DME and switching them to faricimab, and again, as I said for AMD, as I gain experience and see the effect in my clinic, I certainly would consider using faricimab for treatment-naïve eyes as well.

Dr. Do:
Well, it's very exciting we have more choices for our patients.

We're nearing the end of our time together, but before we wrap up, Jack, I'd like to hear, what are your key take-home messages?

Dr. Wells:
Well, I think without doubt the key take-home message is the durability effect of faricimab over our currently available agents for wet AMD and diabetic macular edema. To have 70%-80% of patients on Q12-week dosing or longer in both conditions, in my experience, is much greater than I see in my clinical practice on a day-to-day basis with the medicines we currently use. And finally, there were no safety concerns with faricimab. Specifically, we didn't see any increases in intraocular inflammation [IOI] or retinal vascular occlusive disease or retinitis.

Dr. Do:
Those are great key take-home messages. I also wanted to add that faricimab is the first molecule that blocks both VEGF-A and angiopoietin-2, and we know from our science that too much Ang-2 leads to vascular instability. And by blocking that, we're hoping to promote more stability within the retina, which hopefully can translate to better clinical outcomes for our patients.

I'd like to thank our audience for joining us today, and I'd also like to thank you, Jack, for this great discussion on faricimab. I hope that people will have learned about this new mechanism and then can use this in their clinical practice. Thanks, Jack.

Dr. Wells:
Thank you very much, Diana. I really enjoyed our conversation.

Announcer:
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