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

Frontiers in Diabetic Macular Edema: Durable Suppression for Addressing Health Disparities

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Frontiers in Diabetic Macular Edema: Durable Suppression for Addressing Health Disparities” is provided by Prova Education.

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Dr. Weng:
Unfortunately, racial disparities exist in the treatment of diabetic macular edema, and this commonly leads to poor outcomes. We know that regular anti-VEGF treatment is key to maintaining vision, but are there new targets that can provide a more durable treatment response?

This is CME on ReachMD. I’m Dr. Christina Weng, and joining me for today’s discussion is my friend and colleague, Dr. Arshad Khanani. Arshad, welcome to the program.

Dr. Khanani:
Thanks, Christina. It’s great to be here.

Dr. Weng:
Great to have you. Well, Dr. Rishi Singh has new research that underscores how the progression of diabetic macular edema, or DME, depends not only on screening and treatment, but also on disease burden and access to healthcare. Can you briefly review what his data showed?

Dr. Khanani:
Yes, Christina. He did a very interesting study. What they did was they characterized association between socioeconomic factors and anti-VEGF utilization and looked at the outcomes in patients with DME. And what they found was that baseline visual acuity is worse in Hispanic populations versus White populations and patients with Medicaid. And the visual acuity outcomes are actually worse in Hispanic and African American versus White population and patients with Medicaid. So I think the bottom line, Christina, is that – and we are very aware of this in our practice – that there’s less access to care, which leads to fewer injections, which leads to poor outcomes, again, highlighting the fact that patients need to be treated frequently to have good visual outcomes when they have diabetic macular edema.

Dr. Weng:
Absolutely. I think that really nicely reiterates it from a very objective standpoint. And I agree with you, Arshad, that I see this especially at the county hospital where I work, where there is a larger proportion of patients from ethnic minority groups as well as lower socioeconomic status groups. So we do see that, and other studies have corroborated what was found in Dr. Singh’s study. I’m going to show you on this slide here some interesting data from one study that was published last year that also found that there were racial disparities in response to treatment for DME. And the investigators in this study found that Black patients had a lower odds ratio of vision improvement following initial bevacizumab injections compared to White patients. While the reasons behind this observation are likely multifactorial, what I can say is that it’s very frustrating to see these patients lose vision.

Now the current standard of care in DME is anti-VEGF therapy, and despite this being highly effective, it only targets the VEGF molecule. But we know that other factors are involved in vascular permeability and neovascularization. One of those factors is

angiopoietin-2, or Ang-2, which along with VEGF-A is also elevated in the vitreous of patients with diabetes.

Arshad, can you tell us a little bit more about this molecule? What is Ang-2?

Dr. Khanani:
So Ang-2 is, as you said very nicely Christina, is elevated in disease vessels. So in normal vasculature, you actually have Ang-1 which does stabilization of blood vessels by activating Tie-2 receptors. So what happens in diseased vessels is what's called the angiogenic switch, where you have higher level of Ang-2, which leads to dephosphorylation of the Tie-2 receptor, which in turn leads to vascular leakage, destabilization, and inflammation. And as you suggested, we have data from vitreous from patients with diabetes as well as AMD and RVO that Ang-2 levels are activated. So basically, it's synergistically working together with VEGF in disease vessels, leading to leakage, inflammation, and pericyte loss. And I think the key here, Christina, is that can we block Ang-2? Can we improve outcomes in our patients with diabetic macular edema by going beyond just VEGF-A inhibition?

Dr. Weng:
That's really interesting, Arshad. So I hear about this new molecule, faricimab, which targets both VEGF and Ang-2, which you just told us is also an important part of the angiogenic pathway. Can you tell us a little bit more about faricimab, how it works?

Dr. Khanani:
Yes, Christina. So it's exciting that we are going beyond VEGF inhibition, as I said. So faricimab is actually a bispecific antibody. It's the first bispecific antibody designed for ophthalmology, and it has 2 arms. One arm binds Ang-2, the other arm binds VEGF-A. And then the Fc portion has some mutations that are designed to decrease inflammation as well as systemic exposure. So very exciting molecules, really leading to dual inhibition of VEGF-A and Ang-2.

Dr. Weng:
It's great to hear about investigational therapeutics that have a different mechanism of action from what we currently have.

For those just tuning in, this is CME on ReachMD. I'm Dr. Christina Weng, and joining me today is Dr. Arshad Khanani. We're talking about how we can potentially decrease the treatment burden of diabetic macular edema by targeting new pathways beyond VEGF.

So faricimab, Arshad, sounds like a really promising agent, with its ability to target both VEGF-A and Ang-2. What clinical evidence do we have for using faricimab in the treatment of DME? Can you update us with the latest phase 3 data?

Dr. Khanani:
Yes, Christina. So I think the good news is that we have a large amount of phase 2 data that led to the design of the phase 3 YOSEMITE and RHINE studies in patients with DME. These studies are global, randomized, double-masked studies that looked at efficacy and safety of faricimab compared to aflibercept in patients with diabetic macular edema. So there were 3 different arms in this trial. Number 1 was aflibercept per the label, with 5 loading doses followed by q8-week treatment. The other arm was faricimab q8-week dosing. And then the third arm was personalized treatment interval, which is a very novel way to actually treat the patients more like what we do in clinic, where we control the disease and then we extend those patients based on their needs. And that's what was done in this trial. So of course the primary endpoint of the trial was noninferiority in terms of BCVA gains from baseline in faricimab group compared to aflibercept. The primary endpoint was actually averaged over Week 48, 52, and 56, so that there's no bias about which treatment interval you are in. You know, these studies recruited fast, and patients stayed in this study; the discontinuation rate was low. COVID-19 impact was not significant, and basically, the bottom line was that the studies met the primary endpoint, where the visual acuity gains with faricimab q8 week or personalized treatment interval were similar to q8-week aflibercept.

I think the key here, Christina, is how can we differentiate in terms of what inhibition of Ang-2 is doing compared to just VEGF-A? So you see that effect in CST [central subfield thickness], where we see that there is change in CST from baseline through Week 56, that consistently favored faricimab compared to aflibercept. So patients who received faricimab actually had drier retinas compared to aflibercept. And that was also seen in looking at patients who had absence of DME, where patients treated with faricimab had less DME compared to aflibercept, and then also absence of intraretinal fluid, so were all better anatomic improvements compared to aflibercept. But also, the durability – I think that's another unmet need is durability, where patients don't want to get frequent injections. Over 70% of patients in YOSEMITE and RHINE studies were on at least q12-week dosing interval at Week 52. And of course, safety is crucial. And what we saw, that safety was comparable between the group that was slightly increased rate of intraocular inflammation in the faricimab group, which was 1.3% compared to aflibercept, which was 0.6%. So I'm really excited about having faricimab available to help our patients with diabetic macular edema.

Dr. Weng:
Excellent summary, Arshad. And that's really exciting data to see. I mean, for more than half of the patients in the faricimab arm to be able to reach a q16-week treatment interval at 1 year suggests that this could offer a meaningful reduction in treatment burden for our

patients. And it's also encouraging, of course, to see that this agent seems to be well tolerated from a safety standpoint.

Now you mentioned this earlier, but the concept of reaching beyond VEGF makes a whole lot of sense to me since DME is a multifactorial disease. What are some other promising agents that target factors aside from VEGF that are also in the pipeline?

Dr. Khanani:
So when you look at ongoing trials, there's actually many different mechanisms of action that are looking at going beyond VEGF-A inhibition. The 2 that I've been closely involved with and have presented the data on, number 1 is THR-149, which is a plasma kallikrein inhibitor. We know that plasma kallikrein, or PKal, levels are elevated in patients with diabetic macular edema, and as you mentioned, that, you know, up to 30%-40% of patients don't respond to anti-VEGF therapy because it's a multifactorial disease. So we need to look at MOAs [mechanisms of action] that are different. So THR-149 targets PKal, and the phase 1 data showed that it was well tolerated with no dose-limiting toxicities, and then the visual acuity gains were very good. When you look at month 3 after a single injection, it was 6.4 letters. And the visual acuity gains were very rapid of 7.5 letters at day 14. So very exciting. The molecule is now in phase 2 KALAHARI trial, and the trial is currently ongoing.

The next one is THR-687, which is a pan-RGD integrin antagonist, and as we know that integrin antagonists work both upstream and downstream of VEGF, and they have the potential for broader efficacy and really potential to treat diabetic retinopathy as well as diabetic macular edema and neovascular AMD. So the phase 1 trial of THR-687 also showed there was no dose-limiting toxicities, and patients had a rapid increase in visual acuity in the trial and also maintained that visual acuity gains over time. So really exciting. The phase 2 trial for THR-687 is planned to start later this year.

Dr. Weng:
Thank you for that summary and update. It's really exciting to hear about these broadened approaches, and we look forward to forthcoming data.

So Arshad, in our last few minutes, let's make sure our listeners are really hearing us. What is your take-home message for our audience?

Dr. Khanani:
I think, Christina, the bottom line is that we know that patients with DME get undertreated in the real world, and of course there are disparities based on ethnicity and access to care as we discussed earlier. So I think our goal as physicians is to maximize the visual acuity gains in our patients. And that is why it is exciting to have novel mechanism of action to really improve outcomes in patients, and agents having greater durability will help us address that. So super exciting. Hoping that faricimab will be available soon, within the next year or 2, to help our patients, and then of course the other molecules that are coming down the pipeline. So very exciting times for physicians as well as patients.

Dr. Weng:
I totally agree. It really is encouraging to see all of these new mechanisms of action and how efficiently they're moving along in the investigational pipeline as well.

My take-home message that I'd like to emphasize for our listeners is that treatment burden is a huge unmet need in DME, and because of many factors, this issue is magnified even more in minority populations. Faricimab, which blocks both VEGF-A and Ang-2, along with other potential new treatments, which you really nicely covered, may help reduce treatment burden and ultimately improve visual outcomes for our patients with DME.

Well, that's all the time that we have today. I'd like to thank our audience for listening in and thank you, Arshad, for joining me and sharing your valuable insights. It was a pleasure speaking with you.

Dr. Khanani:
Thank you for having me, Christina.

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