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Making the Case for Dual Ang-2/VEGF-A Inhibition: Anatomical Benefits

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Dr. Lim:
Dual inhibition of VEGF and Ang-2 is a new method of managing diabetic macular edema [DME] and neovascular age-related macular degeneration [nAMD]. But what evidence do we have that blocking Ang-2 is beneficial for our patients?

This is CME on ReachMD, and I'm Dr. Jennifer Lim.

Dr. Regillo:
And I'm Dr. Carl Regillo.

Dr. Lim:
Carl, a lot of us have been wondering whether anti-Ang-2 and faricimab is really providing an additional benefit to patients or whether it's perhaps a higher anti-VEGF affinity of this faricimab molecule? We know that there's been some preclinical work that's shown evidence regarding decrease in leakage for the faricimab, compared to the only anti-VEGF-treated eyes. Can you expound on this, please?

Dr. Regillo:
Sure. In fact, there's a lot to support blocking Ang-2 adds to the benefits we see clinically. Let's start with preclinical data, which is plentiful. Preclinical data for Ang-2 inhibition alone and dual-Ang-2/VEGF-A inhibition shows independent and better combined effects regarding in vitro and in vivo models on leakage, inflammation, and fibrosis. And these are a variety of animal models, too, when it comes to in vivo. Mouse studies, mouse spontaneous CMV, laser-induced CMV in primates, all of them point to Ang-2 inhibition having some effect, and that's alone. And then of course, blocking both Ang-2 and VEGF in these models adds to the benefit. So preclinical data, really strong.

Also, there's early clinical testing, clinical trial testing. We see increasing the dose of VEGF inhibition 4x in both neovascular AMD and DME. That was the HARBOR and READ-3 studies with ranibizumab and the phase 3 PULSAR/PHOTON studies with high-dose aflibercept. This did not result in a greater reduction in central foveal thickness with monthly dosing during that loading phase and also didn't show any additional benefits with macular leakage on fluorescein angiography.

Lastly, regarding clinical trial design of faricimab versus standard 2-mg aflibercept, analyses from the matched initial or loading phase monthly dosing in both neovascular AMD and DME trials allows true head-to-head comparison of anatomical outcomes.

Dr. Lim:
Absolutely, Carl. You know, I think this head-to-head phase is really key when we're trying to compare these 2 drugs, faricimab and aflibercept 2 mg in the pivotal trials. And basically, we can look at either the AMD data or we can look at the DME data. And we can look

specifically at either the central subfield thickness [CST] reductions, and we can see that for the AMD data during the head-to-head phases, that the faricimab-treated eyes had greater reductions in the central subfield thickness than the aflibercept-treated eyes. And when we look at components of intraretinal fluid, subretinal fluid, again, there were greater reductions with greater proportions of eyes that had first absence to intraretinal fluid and subretinal fluid in the faricimab eyes than in the aflibercept eyes. And incidentally, it also occurred sooner, by about 4 weeks sooner, in the faricimab than in the aflibercept eyes. And again, this was true in the diabetic macular edema eyes too. When we look at the amount of reduction in the CST, it was greater in the head-to-head phase for the faricimab compared to the aflibercept eyes. And we can also see that this occurred sooner overall in the study as well with greater reductions seen in intraretinal fluid reductions, again, for the faricimab than for the aflibercept-treated eyes in the head-to-head dosing phases.

Carl, when we look at these biomarkers, aside from fluid compartments, we can also look at other anatomical biomarkers such as biomarkers for, say, fibrosis. What's the data, say, in diabetic macular edema with regards to fibrosis?

Dr. Regillo:
Yeah, this was a really interesting post hoc analysis of epiretinal membrane, or ERM, formation in the phase 3 YOSEMITE/RHINE pivotal studies for DME. So in these DME studies, there were lower rates of ERM formation with faricimab, and this was dose dependent, and that was seen at both years 1 and 2 of follow-up. Looking at faricimab dosed every 8 weeks versus the aflibercept dose every 8 weeks, it was 4% with faricimab, 8% with aflibercept, so about half the proportion of patients that were developing ERMs over the course of their DME treatment. And ERM formation is correlated with worse best corrected visual acuity and a greater likelihood of having residual fluid.

Dr. Lim:
Absolutely. I think it's a really important biomarker. And patients also don't do as well, right, when they develop an epiretinal membrane. And I believe, for patients who have diabetes and are treated, on average, about 9.5% develop an ERM within the first year. So I think it's really important that we now have a drug that can also decrease the incidence of the ERM formation, and as we know, result, as you nicely summarized, in better visual acuity and anatomic outcomes with treatment.

What about signs of inflammation? We know that in the basic science studies, in the animal studies, that faricimab led to lower rates of inflammation in eyes in these animal models. Is there a correlate of inflammation in these eyes when we look at the OCT [optical coherence tomography]?

Dr. Regillo:
Yeah, we looked at fluorescein angiographic leakage as one biomarker. Now, that may or may not reflect inflammation, but it certainly reflects vascular incompetence. In the DME pivotal studies for faricimab, there was a greater median reduction in central macular leakage assessed by fluorescein angiography at week 16, compared to aflibercept. Again, that's that matched monthly dosing phase. Also showed greater percent of resolution of macular leakage. So at least with leakage, vascular incompetence, something that we'll see routinely, of course, in patients with diabetic retinopathy, faricimab definitely worked better, pointing again to this sort of dual mechanism of action.

And then there is this interesting reduction in hyperreflective foci volume with faricimab versus aflibercept, again, standard 2 mg. And hyperreflective foci are seen on OCT and are believed to be a biomarker of inflammation.

Dr. Lim:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Jennifer Lim, and I'm joined here today with Dr. Carl Regillo. Today, we're considering the anatomical and biomarker evidence around dual inhibition of Ang-2 and VEGF in the management of neovascular AMD and diabetic macular edema.

Thank you, Carl. I do believe that the faricimab hyperreflective foci reductions and the faricimab reductions in leakage do reflect the fact that there's an anti-Ang-2 inhibition in addition to the anti-VEGF.

Let's now consider some hypothetical cases. For instance, Carl, how would you manage a patient with severe NPDR and macular edema with good vision of 20/30 and, say, a central subfield thickness of approximately 300 µm?

Dr. Regillo:
Well, the primary goal of treatment here is to resolve the macular edema. Visual acuity is not so bad; by central subfield thickness, the edema is not so bad. And we know when there's mild edema and pretty good vision, as this hypothetical case, we can get a good result with any of the anti-VEGF drugs, any of the drugs you've been using in practice now for years, whether old or new. And with frequent treatment, as we treat the macular edema, because you're going to require frequent treatment at first, we can expect the level of NPDR [nonproliferative diabetic retinopathy] to also potentially improve, at least a little bit, and reduce the risk of it worsening to PDR

[proliferative diabetic retinopathy], which would be of great benefit to the patient. So I actually think in such a case, you could pretty much start with any of the available anti-VEGF agents. And if you're getting a good effect, great, stick with it. If you're not, if you're not seeing a good effect or maybe the NPDR is worsening to PDR, then it might be worth considering a, quote, stronger drug, if you will, and our second-generation, particularly faricimab with the dual mechanism of action, would be suitable as a drug you could turn to or switch to.

Dr. Lim:
Yeah, I agree with you, Carl. And I think in some cases where maybe you're getting an effect but, say, you need frequent treatments to maintain that effect, you might want to consider one of the agents with longer durability, such as faricimab as well.

Let's look now at a hypothetical patient who has severe diabetic macular edema, central subfield thickness 550 µm, there are a lot of hyperreflective foci present, and the vision is about 20/100. How would you approach such a patient?

Dr. Regillo:
Well, in such a case, this is where the ability to dry better really matters. Because it would be greatly beneficial to this patient's visual outcomes to get that macula dry as fast as possible. And, in fact, this was proven in the DRCR [Diabetic Retinopathy Clinical Research] Network Protocol T, where the best drying drug at the time of the 3 that were compared, and it was bevacizumab versus ranibizumab versus standard 2-mg aflibercept, aflibercept dried the best and resulted in the best vision improvement in these eyes that had worse edema and worse vision, accordingly. So now that we have, I'll call it a second-generation drug, faricimab, with its DME studies showing even better drying and faster drying, it makes a lot of sense to apply that same approach here and start with the best drying drug, and that's faricimab right now. And so if possible – now, reality in clinical practice, it may not be possible because insurances may dictate the drug we start with, but I would say if you can start, I would start with faricimab in such an eye. And if you can't start with it, try to switch to it as soon as you can to get the macula as dry as possible as fast as possible.

Dr. Lim:
Yeah, I will agree with you as well, because I think when the retina is really thick, it really behooves us to get it thin and as soon as possible, because as you know, you require a frequent number of injections, more so than if the retina were, say, thinner. And we also know that if we leave the retina thick for significant amounts of time and then switch, you may not get the visual effect. And I think this was shown very early on in RIDE and RISE in the sham arms, where after sham/laser, these eyes were given anti-VEGF. And although the retinas thinned out, it was too late, right? We didn't get the visual acuity. So I think, yes, we need to kind of hit it hard when there's a lot of edema and try to get that down because we know it's going to take a little bit of time, a few number of injections to get that retina down.

Let's turn now to the scenario of a patient who has severe DME. Again, central subfield thickness, say around 500 µm, visual acuity is 20/200. And then on top of this, this is a patient with glaucoma. Does the fact that the patient has glaucoma influence which agent you would use?

Dr. Regillo:
It could. Traditionally, I would have thought of standard 2-mg aflibercept to get the best drying. All the first-generation drugs, it's the same volume. We know that when you inject any volume intravitreally, you're going to get a transient rise in intraocular pressure. So you don't want that rise too high and too many times over time. So ideally, you get the macula dry with the drug with the least amount of treatments and hopefully the least amount of volume.

Now, the only drug that's greater volume than 0.5 mL to administer intravitreally at the recommended dose is the newer high-dose aflibercept; that volume is 0.7 mL. So technically, with slightly higher volumes, you're going to get higher pressures. And you may be less inclined to consider it in a patient like this that has glaucoma.

Dr. Lim:
Yeah, I agree with you. I think those slight pressure rises after an intravitreal injection are kind of like hitting the optic nerve on the head, if you will, and it causes some damage that, over time, if you keep doing this, it builds up. So I think in a patient who has glaucoma, I'd be more inclined to use more of a standard volume as opposed to increasing the volume and using something like 70 µL. I'm one of those rare birds that checks the intraocular pressure after every injection. And, you know, there are patients who even after just 50 µL, do have a significant rise in pressure immediately afterwards, you know, and eventually tapers down to below 30 again. But again, I wouldn't want to risk that in a patient with glaucoma.

Dr. Regillo:
I agree.

Dr. Lim:
Yes. So this has been a really fascinating discussion, Carl. And before we go, what's one thing that our audience should take home with them today?

Dr. Regillo:
Well, the good news is that we have better drugs, better drugs to treat neovascular AMD and DME. And how are they better? They dry better and they last longer. And so I see a time in the future that us, as treating physicians evolving into using more and more of these newer agents, particularly faricimab, to improve our real-world outcomes for both of these conditions.

Dr. Lim:
Yes, and I think the fact that biomarkers also give a consistent story with these newer agents and that we have decrease in the hyperreflective foci. In the case of faricimab we have decreased epiretinal membrane formation, and then, of course, better drying and faster drying with the newer agents compared to the aflibercept 2 mg, that this gives us a nice consistent story and makes us confident in the fact that these newer agents are, in fact, better drying agents and more durable than the standard doses.

So that's all the time we have today, Carl. Thank you so much for being here today and sharing your knowledge with us.

Dr. Regillo:
Thank you, Jenny. It's been my pleasure.

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