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## Are Two Pathways Better Than One? Experts Discuss the Role of Ang-2/VEGF-A Inhibition in Retinal Vascular Disease

### Announcer:

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### Dr. Khanani:

Hello, and welcome to this CME webinar, "Are Two Pathways Better Than One?" This is an expert discussion about the role of Ang2 and VEGF inhibition in retinal vascular diseases. I'm Arshad Khanani with Sierra Eye Associates, and I'm lucky to have two of my great colleagues and friends here, Dr. Karl Csaky from Retina Foundation of Southwest in Dallas, Texas, and Dr. Christina Weng from Baylor College of Medicine in Houston, Texas. Welcome, Christina and Karl.

### Dr. Csaky:

Thank you, Arshad.

### Dr. Weng:

Thanks, Arshad. Great to be here.

### Dr. Khanani:

I'm looking forward to our discussion today about new treatment options for our patients, especially targeting additional pathways beyond VEGF-A inhibition. And we know that over the last several years, we're widening the treatment options for our patients. And looking at novel treatments for neovascular AMD, DME, and RVO, I think, as a field, we are looking at greater durability. As we are aware that faricimab, the first bispecific antibody that blocks VEGF-A and Ang2, was FDA approved almost 2 years ago. And recently, we have seen the approval of aflibercept 8 mg. And obviously both of these treatments are designed to achieve better durability. But I think the goal of the discussion today is to see if we are seeing benefits with additional inhibition of Ang2 in the clinical data set, in the real world, and of course, discussing the outcomes, and really considering that we treat a lot of patients. Seeing the patient cases today in this webinar, I'm looking forward to our discussions. And of course, we know a poor delivery system also provides durability. It's a surgical implant that releases ranibizumab over time; it was recalled because of the septum dislodgement issue, and then now it's back in clinical trials using a new implant and a new refill exchange needle.

So here's a polling question.

Alright, so let's get started with the first talk, dual inhibition therapy, a novel mechanism of action that addresses retinal vascular disease pathophysiology more comprehensively than anti-VEGF therapy. So, Karl, you want to get started?

### Dr. Csaky:

Well, thank you, Arshad. Yes, we're going to talk a little bit about first, some basic science of this idea is attacking one kind of bad protein better than just attacking VEGF? And this really gets to the kind of basic science of the angiopoietin system. And it turns out that through lots of research, there are additional proteins that seem to be involved in this vascular instability issue where we get leakage and bleeding and vessel growth. And it turns out that the angiopoietin system, especially angiopoietin-2, is an important player, both as with its own mechanism through the Tie2 receptor, but also probably equally as important; it acts synergistically with VEGF. So clearly, there's plenty of basic science data to show that angiopoietin-2 seems to be an important player.

And in fact, when we look at some of the animal data as it relates to, for example, leakage, when you start to inhibit the Ang2 system in addition to VEGF, you just get better overall control in various animal models. And of course, what's really exciting as we think about the clinical application is this role of inhibition of angiopoietin-2 in fibrosis and the mechanisms behind fibrosis that we see in patients.

Now what's clear is that when we think about the inhibition of both angiopoietin-2 and VEGF, we can look at the kind of predicted PK, and this is actually done from the clinical data that we generate. We can get aqueous samples, and we can look at the degree of suppression of these proteins. And of course, it turns out that the suppression of angiopoietin-2, in some ways, is more durable and longer than the VEGF. And again, because of this potential synergistic approach that Ang2 has on VEGF, it might actually then explain some of the increased durability and the effects, especially on leakage, that we'll talk about later on.

Again, when we think about this combination therapy, this has been tried individually, even beyond what we'll see as a bispecific when we add nesvacumab, which is a specific anti-Ang2 antibody, to aflibercept. This was in the RUBY study, when we look at the data again, you start looking at the degree of drying, of the ability to remove fluid, that combination seems to do better than aflibercept alone. So a very important aspect.

And interestingly, when we tried to do this in prior trials, for example, in HARBOR, where we simply tried to increase the amount of ranibizumab, we didn't see that effect. And interestingly, that was in the case of neovascular AMD. Also, in the most recent kind of higher doses of aflibercept, the PULSAR, similarly, we

did not see a benefit on additional drying. When we look at DME, we see a similar kind of interesting phenomenon. And it turns out that, in fact, when you look at the degree of drying in DME with increasing doses of ranibizumab, the lower dose, to some degree, performed a little bit better. And then in PHOTON, which is the high-dose, 8-mg aflibercept equivalent in DME, we again, did not see that benefit that we see with dual inhibition in the RUBY trial.

So again, in many ways, understanding this important role of inhibiting Ang2 is very critical. And of course, it's really important to recognize that we don't see Ang2 inhibition with aflibercept. Here are some aqueous human samples from trials where we looked at Ang2 levels with either faricimab or aflibercept, and clearly it's only when you use faricimab do we see inhibition of Ang2; we don't see that with the aflibercept. So clearly, this bispecific molecule is very potent and very good at inhibiting both VEGF, but most importantly in this discussion, the Ang2 pathway.

And then, of course, there have been additional pieces of information. As we start to look at the extent of what dual inhibition could do, we start to understand that there's more than just potential control of vascular leakage, which was a critical clinical aspect of this dual inhibition, but there's also reduction of inflammation. Ang2 has a very important role in inflammation as well as in fibrosis, and we see that aspect in our clinical studies with reductions in these hyperreflective foci we see in DME and the reduction in retinal membrane formation in DME as well, again, with dual inhibition.

So overall, I think there's lots of evidence to suggest that this dual pathway does something a lot more than what we see with just anti-VEGF inhibition alone.

So I guess, you know, let's just throw this back to Arshad and Christina, and just kind of get your thoughts. You know, there's all of this clinical trial data that I think is very elegant; I'm kind of curious as to your take and, you know, what strikes you about this dual inhibition data that's been presented?

**Dr. Khanani:**

I think, Karl, a great overview of the data we have so far, and we're going to dive into clinical trial data also later. But I think, to me, the proof is in the pudding, right? So when you have patients in your clinic that have disease activity, and if you introduce a new agent that is now dual inhibition, can you see outcomes that are better? And so when faricimab first came out, you know, I was using it in patients who were very high need and getting that anatomic response in those patients that had been chronically treated with anti-VEGF-A agents, that was the real wow factor for me. And it happens very quickly with neovascular AMD right off the gate. In DME, sometimes it takes a few doses to suppress those levels, DME being more inflammatory, and there are more cytokines involved there. So that was my clinical, you know, experience when faricimab first came out. I don't know what Christina's experience is.

**Dr. Weng:**

Yeah, thanks. That was a fantastic overview, Karl. You know, it's interesting because we've been so VEGF-centric for the past two decades in our community, and that's thanks to the remarkable and revolutionary effect that our first generation anti-VEGFs have had for these common conditions and the patients that we see. So we're all very grateful to that.

It's easy to think though that more is better, you know, and sometimes we forget that there are many other inflammatory cytokines and molecules that are involved in the pathogenesis of these diseases. So what really I found compelling was a slide you showed where we looked at fourfold doses of ranibizumab and aflibercept and saw that there wasn't a significant improvement in the central subfield thickness in those trials that you showed, and yet that is what we're using to guide management. So you know, while people will sometimes point and say it's impossible to dissect the effects of the VEGF blockade versus the Ang2 blockade in a drug like faricimab, for example, I think that is really compelling evidence that you showed that there is indeed an effect, a positive effect, that we're seeing from the anti-angiopoietin-2 mechanism of action of faricimab.

**Dr. Csaky:**

And I agree. And I think, you know, as we go through this discussion, I still think we're only at the very beginning of understanding what is going to be, not just the short term, but I think we're still too early in the kind of the conversation, because I'm really more excited about these long-term datas that will be generated with more long-term Ang2 inhibition because that's many times when we start to see anti-VEGF treatments fail. So I think we're just on the cusp of understanding this new kind of era in therapies, where we're starting to attack not just VEGF, but also Ang2.

**Dr. Khanani:**

Thank you, Karl, that was a great overview. And I agree with you; I think long-term outcomes obviously are very interesting for all of us because, as you said, patients end up losing vision and can dual mechanism treatment that controls the disease better than standard of care VEGF inhibition, as well as achieving greater durability and decreasing treatment burden, will that eventually lead to better vision outcomes? I think that's something we need to continue to look at.

So let's move on to the next section. It's initiating novel therapy in treatment-naïve patients. Christina, you want to get started?

**Dr. Weng:**

Thanks, Arshad. Great to be here with you and Karl. It's fascinating when we look at new drugs that enter our field. We've had a lot of them over the past couple of years. A lot of times it's natural to think, well, let me try this for my most refractory patient, the one that I have not been able to get dry. And I think you alluded to that during Karl's section, Arshad. And absolutely, that's a fantastic application of our new therapeutics, especially one that brings about a new mechanism of action, like faricimab.

But it's also so important to remember that treatment-naïve patients are also excellent candidates, and in fact, for many different reasons, they are potentially patients that might even respond better to these types of therapies. So what I hope to do in this section is take you through several real-life cases. There's a few patients of mine and one of Dr. Khanani's as well, and then we'll have some discussion about them.

So this is the first one here. This is a 62-year-old woman with longstanding non-insulin dependent diabetes mellitus, presenting with blurry vision in her left eye. You can see her A1c is 8.7. And depending on what region of the country you're from, you might think that's good or bad. That's pretty good for Texas. I know that Karl can attest to that. But she had no history of treatment or surgery. She's a non-smoker. She works as a manager of a very busy restaurant. And I mention that because, in general, a lot of our patients with diabetic macular edema, which is what this patient had, have many other obligations in their life, and many other physician's appointments that they have to make as well. And that really plays in to one of the factors that I consider when I'm developing a treatment plan for a patient. So keep that in mind that she has a very busy lifestyle. Still working. She's not on insulin. She's taking metformin and doing the best she can. So like I said, A1c of 8.7. Her visual acuity is 20/40 +1. She does have moderate NPDR, and you can see on her OCT that there's absolutely some intraretinal fluid that's very clear to see there.

So what I started her on was actually faricimab for this patient, just keeping in mind the need for durability in this particular person. And so here she is after the first faricimab injection. You can see there already is some improvement, still a little bit of intraretinal fluid cystoid changes that you see there, but she already appreciated a slight difference in improvement in her visual acuity. So we kept going.

I brought her back again in another 4 weeks and treated her once more. And here she is; she made another jump in her visual acuity. You can see the CST is also decreasing. Here she is again 4 weeks later after faricimab #3. Continued improvement there. And then I

gave her a 4th faricimab injection, and then decided to extend her out to 8 weeks. And you can see that she's really improved. She's at 20/25 +2, with really barely any fluid that can be seen now on the OCT.

So before we jump into the discussion, here's a polling question.

And here's another polling question.

And I'd like to now include my co-presenters here for this roundtable discussion. I think there's a lot of different factors to potentially look at here in this study, but maybe I'll turn it to Karl first in asking, you know, this is a patient that had DME, was treatment naïve. There's a lot of different anti-VEGFs to choose from now, and I shared with you some of the reasons for why I decided to start with faricimab in this patient who is very busy and still employed. But how do you choose which patients might be good candidates for certain specific anti-VEGFs? And keeping in mind, of course, that most patients were treatment naïve in the major trials. So in YOSEMITE and RHINE, the phase 3 registrational trials for faricimab, in the indication of DME, about 75 percent of those patients were treatment naïve. And we've also seen from several real-world studies, major ones like TAHOE and FARETINA-DME, that in the subset of treatment-naïve patients from those studies, they also had a pretty substantial response and improvement in visual acuity and central subfield thickness.

So Karl, how do you make that decision?

**Dr. Csaky:**

Yeah. I mean, I think the part of the data that I find to be most helpful, in addition to trying to understand, you know, the durability, but is the rapidity with which the fluid can go away. I think that's a very important feature that we don't want these patients to just continue to have to come back when there is a certain degree of uncertainty is how well they respond. And I like the ideas, I like when we see these patients back, even after just 4 or 5 weeks, even after one injection, we tend to see a really good response in their fluid status. And I think that I find that to be very helpful, especially in patients, because they're worried about, you know, what does this really mean? How many injections am I going to need? And I think to be able to show them a very good, robust, rapid response can be very helpful. And I know in the past, it's been sometimes frustrating when we've been using injections and you get these very small, incremental improvements. As opposed to with faricimab, which sometimes you can get like you had in this case, had a much more dramatic improvement. So I find that to be very helpful as part of my kind of decision-making on what to start with.

**Dr. Weng:**

I really appreciate one thing you said especially, Karl, and that is that the rapidity of drying is something, it's sort of like that fourth dimension or fourth factor that sometimes we don't talk about enough. You know, time is everything, right? So the better and faster you can restore visual acuity for patients, the drier you can get them in a shorter amount of time, that's very meaningful in many ways. So I appreciate that, and I have seen that with faricimab use in some of my DME patients.

Arshad, you're the creator of these very important real-world studies, TRUCKEE, which we'll talk about later, but also TAHOE. But most of the patients that I've seen in the data you've presented so far were actually not treatment naïve in TAHOE. Do you use faricimab for treatment-naïve patients? Do you think that that is an appropriate application?

**Dr. Khanani:**

No. Christina, I think the key is just to follow up on what Karl said, is what is the best agent we can utilize for the patient that's sitting in front of you that can give you the best anatomic outcomes in controlling disease activity? As you mentioned, if you have persistent disease activity, it leads to neurodegeneration, leads to visual acuity gains that are not as good as if you can dry that fluid. So, you know, in TAHOE, obviously the naïve patient subset is smaller than previously treated. Because, as you said earlier, I think once physicians see that, even in treatment-resistant patients, you can see improvements with dual inhibition, then the naïve patients is actually easier. So I'm actually using faricimab as a first line for patients with DME that come to my clinic. Of course, there are payer limitations and other things that can happen, but if I don't have those limitations, I am using that at first line because that's what I would want for my own eye. Because you are going beyond that VEGF-A inhibition, and you're optimizing the outcomes in terms of disease activity.

**Dr. Weng:**

Yeah. Thanks a lot, Arshad. And just one final question before we move on to the next case, Karl, but these new longer-durability clinical trials that are being run are progressively more complicated than ever before. And, you know, the question really arises a lot when you have these drugs in the real world is, do you follow that when you're looking at extending? You know, as you can see from what I did for this patient, I attempted to follow sort of that PTI, or personalized treatment interval, arm of YOSEMITE and RHINE where they got four

monthly injections and then they were able to be extended after that. Is that something you follow closely? Or are you more conservative? And a lot of my colleagues are using 2 weeks at a time, as we're used to doing for so many years.

**Dr. Csaky:**

Yeah, I think, you know, it's really challenging to follow the guidelines, right? Because these monthly injection regimens can be quite challenging. And especially as we just talked about, when you start to see a robust response, you want to really start to extend sooner than per the protocols. So, you know, I think this is something that's going to be an ongoing discussion, this mechanism of action, how much does it take to really generate the full response? Is something that I think will require some more interrogation in the real world. Because I think, you know, there'll be many people who are not going to follow the full regimen of the trials. And I think we'll need to see what happens when we start to reduce the number of what we call loading doses in these patients.

You know, we did this with anti-VEGF as well. You know, we quickly transitioned over time to fewer and fewer loading doses, and it didn't seem to have a big impact on the ultimate efficacy. And right now, you know, the impression I get is that we don't necessarily have to follow the full regimen, but I think it remains to be seen long term what the outcomes will be.

**Dr. Weng:**

Yeah. Thanks, Karl. And Arshad's studies, TAHOE and TRUCKEE, both show a pretty compelling effect in some patients after just one, two, or three injections, so that's really interesting to see.

Let's move on to the second case study. I want to show you now in a different disease state. This is a treatment-naïve patient with wet macular degeneration, 75-year-old, long-term patient of mine. I've been following him for 10 years. He's actually a physician. It's always the physicians that get you. And I had just seen him, you know, I see him every 6 months. I had just seen him 4 months prior, and suddenly he comes back with metamorphopsia and change in visual acuity in his right eye. And as you can see in the OCT, that is what I saw 4 months prior at the top, there and then, now he comes back, and indeed, there's some subretinal fluid suggestive of a conversion to exudative wet macular degeneration. He is a non-smoker. His baseline is 20/20, and he was coming in at 20/40 extremely bothered.

So again, I started this treatment-naïve patient on faricimab, and I just want to show you what a remarkable response he had after a single injection. Really, you don't see any residual fluid there, and his vision's already improved back to 20/25. I treated him again on a monthly basis up until the fourth injection. And then I was more conservative with him; I don't know if it was the physician effect or what, but I did extend by 6 weeks. Excuse me, I extended by 2 weeks to a 6-week increment. And there he is at 20/20, at the bottom there. And then we kept going. You know, you'll see me extend now to 8 weeks, just sort of baby-stepping him out. But he had no fluid returned, except that very first visit that I saw him, and he's now at every-16-week injections, which is a very doable for his busy lifestyle. And he's back to his baseline of 20/20.

So before we jump into the discussion, I want to show a polling question to the audience.

And I want to start off with Arshad this time around. You know, same types of questions that arise here, right? In phase 3 TENAYA and LUCERNE, that's different from YOSEMITE and RHINE, the companion DME studies, phase 3 TENAYA and LUCERNE, we're looking at wet AMD patients, and all of them, 100 percent of them, were treatment naïve. And that goes back to the point I mentioned earlier again is, you know, we tend to use these for the worst patients of ours, the most refractory patients of ours. But in fact, the best data we have from these phase 3 studies is from a treatment-naïve population. What factors do you consider, Arshad, when you're thinking about using faricimab as a first-line therapy for your patient with wet macular degeneration?

**Dr. Khanani:**

A great case, Christina. I think it really highlights several points, and that's what I use in my clinical practice as a guide to use faricimab as first-line agent. Number one is rapid improvement in anatomy. And I think you saw that the fluid disappeared after one injection, which can happen with other agents, but this is very consistent in my clinical practice. And your patient had mild disease. You know, a patient with subretinal hyperreflective material, subretinal hemorrhage, a lot more disease activity, PED, intraretinal fluid, all the signs of bad disease in many of those patients, and they go away. The disease activity is completely gone after one injection. So I think that's where the power of Ang2 inhibition comes in with VEGF-A inhibition.

And that's why I actually use the TENAYA and LUCERNE as a guide for my naïve patients. So I do load just like you did. And I think that may or may not be needed, as Karl alluded to, and there was DME in here, too. But what I do is I actually extend 1 month at a time. I know you did 2 weeks just to be cautious. And the reason I do 1 month at a time is that if I've achieved disease activity control after one injection, I've loaded them three or four times, and now they have no disease activity, I'm very confident that it's not coming back based on TENAYA and LUCERNE. But it's that power of disease activity control, drying up effect, anatomic benefit that's rapid, I think those are the primary drivers for me to actually use faricimab as first line for naïve patients with neovascular AMD.

**Dr. Weng:**

Perfect. Thank you. And your response is perfect because it also tackled what I was going to ask you about, how you extend. And I find that there's a lot of heterogeneity within our peer community with how people are doing that. Karl, are you extending and contracting by 2 weeks at a time? Four weeks at a time? What do you do?

**Dr. Csaky:**

Yeah, so to be fair, I still use standard anti-VEGF agents. And I use faricimab as first line in what, you know, Arshad was saying, these more difficult anatomic cases, right? And in those cases, I'm much more cautious to extend more rapidly, so those are the cases where I really want to load up because if they come right out of the block into my clinic with PEDs, lots of subretinal, you know, reflective material, poor vision, I have this sense that they have just worse, aggressive disease, and then I'm much more likely to really be aggressive, and then extend, you know, much more slowly, especially if it's their only eye, every 2 weeks because I really want to control this severe disease and not have that severity come back. So I'm very much driven by the degree of severity of the anatomic presentation when the patients come in.

**Dr. Weng:**

Yeah, perfect.

**Dr. Khanani:**

I have a quick question for Karl. So Karl, you said that you use traditional agents; is that because of payer reasons? Because to me, whether you have mild disease or severe disease, you would want to use the most potent agents. I was just wondering why would you start with VEGF-A inhibitors? And they're great and they're safe. Obviously, we have not seen any safety differences with faricimab either. But just curious, like, you know, most of my patients have good coverage, and that's why I can use faricimab at first line. I know in Texas, it is not as common, so what were the key reasons for not using them?

**Dr. Csaky:**

I think, you know, a lot of this just has to do with the long historical comfort level of, you know, kind of knowing, having this experience with aflibercept primarily. I mean, that's the most common anti-VEGF agent that I'm going to use. And so it's really a question of, you know, the degree to which we don't yet have that long-term faricimab data. And if I feel like it's a relatively small CNV that, in general, are the ones that we know, even historically with anti-VEGFs, can do quite well, so I'll start with that, and then if I need to, switch to faricimab.

**Dr. Weng:**

Karl, I really appreciate that perspective, because this was a patient who, obviously, you can imagine, had done a lot of research already and came in with a faricimab handout asking that he wanted the newest agent. And that's what we did for him. But I do think that someone with this mild of disease may have responded just as well to any of our first-generation anti-VEGFs, which are very effective. So I appreciate that view for balance. What I love about faricimab map is that it's on-label to extend all the way out to q16. And even though you're, of course, free to do that with any of our first generations, that always gives me that additional comfort to say, 'On label, we can take you all the way out to every 4 months, which is only three times a year once you're loaded.' And I think patients really like that. So appreciate both of your views.

Alright. And this final case I want to share is a 61-year-old man with poorly controlled insulin-dependent diabetes coming to me with blurry vision in his left eye. No surprises, you can see from the OCT that he has pretty significant DME. His last A1c was over 10. He has no history of treatment, and he was also found to have PDR on his examination. And it's always amazing to me how well these patients can see through some pretty bad-looking retinas. This man was actually still 20/40 -1.

Here's a polling question.

Let me just run through and show you how this patient responded to faricimab. So here I am treating him on a monthly basis, and you can see that he has slow, incremental improvements with every injection, and also slow incremental improvements in terms of his visual acuity. And here he is after five faricimab injections, still about 20/30 -2. After the eighth injection, finally, even though he still has some fluid on his OCT, he's improved to 20/25 -1, and he's a lot happier.

So here's a polling question before I conclude with just a couple of points that I want to make from this case.

So again, back to YOSEMITE and RHINE, the phase 3 studies that brought the indication for DME to faricimab's label. I want to point out

one thing in these heat maps that are showing the distribution of intervals between the injections. You can see at the very bottom, less than 10 percent, I think it was about 7 percent of patients in RHINE, you can see that there is a small fraction of patients who aren't ever able to extend beyond monthly, beyond every 4 weeks. And I think this patient that I just showed you is one of those patients. So it's important to remember that even though these longer durability drugs work very well for certain patients and allow them to go up to q16 weeks, not everyone is going to have that same experience, especially in such a heterogeneous disease as diabetic macular edema. And again, what I also really appreciate about the label for faricimab is that it allows us that flexibility to go and treat somebody on a monthly basis if they should need it. And it's just important to keep that in mind when you're treating patients.

Here's a polling question.

And then to end this section, I'm going to hand things off to my co-presenter, Arshad, who's going to take us through a treatment-naïve case of a woman with RVO in her right eye. Arshad?

**Dr. Khanani:**

Thanks, Christina. Excellent presentation.

And I think the key is that this new option for diabetic macular edema and neovascular AMD, we have experience for almost 2 years. Now for RVO, our experience is obviously limited. The FDA approval came about 5 months ago. So I'm now experiencing faricimab in patients with retinal vein occlusion. So this is a 58-year-old female, naïve patient to me, came in January with visual acuity of 20/40. And here you can see the baseline OCT, as well as infrared, you can see there's a lot of hemorrhage, lot of intraretinal fluid in this patient. And I think the key is that this patient was treated with faricimab as a first line. And the reason for me is the macular leakage data that we saw in the first 6 months from the BALATON and COMINO study. As you recall, these are phase 3

trials looking at patients with BRVO, HRVO, and CRVO, and patients were treated with monthly aflibercept 2 mg or faricimab. And what we saw was visual acuity gains in the first 6 months and CST reductions were comparable. But as was shown earlier, because of Ang2 inhibition, there was stabilization of macular leakage, where a significantly large proportion of patients that were treated with dual inhibition had decreased or absence of macular leakage compared to aflibercept. So this is a new indication for faricimab, and we are still experiencing. We have not launched a real-world study on it. I don't know if we will, if we have capacity, but we will try to collect some data and present in the future. Christina and Karl both, have you started using faricimab in retinal vein occlusion? Or is that too early?

**Dr. Weng:**

I'll start. I haven't yet, Arshad. That was a great example of somebody who I might consider just because of the sheer amount of fluid that you saw on the OCT. I haven't had a chance to use it in the RVO patients yet, but looking forward to it.

**Dr. Csaky:**

Yeah, and same here. And I think the part that I'm really kind of excited to see is the long-term durability data, because I think that's where, you know, the vein occlusion patients are the most challenging when it comes to the durability issues. And I think that's going to be the real kind of impact factor, I think, that's going to drive its utilization.

**Dr. Khanani:**

No, I agree with you. And I think the data Ramin presented from 24 to 72 weeks where all patients after 6 months were switched to personalized treatment interval with faricimab appears to give that signal. And I agree with you, Karl, I think in real world we need to see if we can see the durability reflect, and I think that's going to really highlight the benefit of dual inhibition.

So let's move on. Our next topic is switching from conventional anti-VEGF therapy to novel treatment. So, Karl, you want to get started?

**Dr. Csaky:**

So here's a case, a patient of mine, 70-year-old lady who again, treating for a long time, 6 years, in this case, aflibercept. And again, a lot of these patients do well. She's on about every 5- to 6-week regimen, doing well. And then, of course, what happens, it's not uncommon with these patients, is that over time, they start to lose some of that efficacy, their vision gets a little worse, and they start developing some persistent fluid. In this case, she had persistent subretinal fluid. And you know, while there's some debate about the impact of subretinal fluid, I think all of us would prefer that a retina be dry. And so there are different steps we can use. We can try to give every 4-week injections, we could try to switch to ranibizumab. And so, you know, we did all that, and yet, despite that, this fluid did not go away.

So let's go to a polling question for this.

Okay. And in this case, you know, I think this is where the benefit of dual inhibition can really shine. And you know, you don't have to worry about steroids or anything else, and you don't have to worry about like in the old days where we had to worry about every 2-week, injections with intermitting with Avastin, and we had all these kind of difficult approaches with anti-VEGF. Here, to me, it's a very kind of simple solution; just go ahead and dual inhibit. And that's exactly what I did. And not only did we get now the resolution of the fluid, but we can now start to extend. And she's now at every 8 weeks with a dry fluid and improved vision. So for me, this is one of the real kind of powers of dual inhibition, is it really does benefit these patients who clearly start to lose the efficacy of single anti-VEGF inhibition.

**Dr. Weng:**

Thanks, Karl. That was a great case, and I think it really highlights a couple of really important points. The first point that you said that I really appreciate is that there is a debate in the community right now about stable subretinal fluid, especially when it's a small amount like that, whether it can be tolerated. And I'm with you, I think there is some convincing prospective data, but that we don't quite have that puzzle figured out yet, and how much fluid is okay, and when is it okay to tolerate fluid versus not? And all else equal, I definitely prefer a drier retina. So I'm so glad that you addressed that point. And for whatever reason, there are just some patients after a longstanding period of time that will start to become active again.

It's also important to remember that the diseases are dynamic, right? So it's not like a patient who might have been fine on a q8-week injection interval, it doesn't mean that, you know, they might be on that forever, some of them are. But the diseases are constantly evolving, and so I'm just so happy that we have other agents to turn to. And I think this was a perfect example of exactly what I would do is look to dual inhibition. And I think it speaks to the fact that the dual inhibition mechanism of action here probably did some benefit and was accounting for that drying up of the fluid that we had seen.

**Dr. Csaky:**

And Arshad, do you have kind of criteria in your own mind about when you're going to switch?

**Dr. Khanani:**

Yeah. So obviously, anatomy is the first one, so if they cannot be dry at 4 to 6 weeks with other agent, then clearly a discussion comes in terms of controlling the disease. And that's what we have seen in TRUCKEE, just like what you showed here, the one injection of faricimab leading to about 1/3 of patients going completely dry that were previously treated with persistent fluid.

And then, you know, so the first for me switching was high-need patients or patients with persistent fluid. Then I started using it in naïve patients, as we discussed. But then the last patient subgroup that you are talking about is actually also an important subgroup where they have to come in every 6 weeks or every 8 weeks for the rest of their lives. And they've been doing that, but they will miss visits or something will happen, and many of the patients are now asking proactively about this new drug that can go every 4 weeks that their neighbor is on or they saw it somewhere. So I think now I'm in the process of switching those patients who are stable at 6 to 8 weeks, if they want to switch. Obviously, we have a track record of safety and efficacy with other agent, and if these patients are happy with them, I'm not going to switch them. But many of them would like to go longer. So now that's the population I'm working on in terms of switching. But anatomy first, then treatment burden, and in the middle, of course, the new patients.

**Dr. Csaky:**

And, of course, you know, the million-dollar question is, when you switch, do you just do like we did in the old days, where, like here, we just switch and start to extend? Or do you all feel as if you've got to go back and do the reloading regimen? You know, I'll just tell you my bias; I don't. If I see a good response immediately, I will start to extend. But I'm curious as to your all's thought process in that switching mode. Christina, why don't you share with us your thoughts?

**Dr. Weng:**

Yeah, Karl, I used to be more of a purist in the sense that I would say, 'Hey, if it's a new drug, we're starting. We're loading you up with four injections again and then extending slowly.' And I have really shifted over the past year to do exactly what you do. So if they've been on a q6- or q8-week regimen, and they don't have a lot of new emergent fluids, such as in this case, I'll often say, 'Hey, do you want to let's start you on every 6 weeks, are you agreeable to that?' I'll explain it to them, and I'll let the patient also guide us because we don't have definitive data at this point for what we should do in those switchers. But I find that a lot of patients will do very well, especially when they respond better to faricimab, they may be able to start at 6 or every 8 and dry up completely, and then we can extend from there. So they love being able to extend those intervals as quickly as possible. So I do exactly what you're saying now.

**Dr. Csaky:**

Arshad, how about you?

**Dr. Khanani:**

So I used to do that when I first started using it. And then looking at my experience and looking at TRUCKEE, I'm doing things a little bit differently. So obviously our goal is not to increase treatment burden. So if somebody is on every 6 weeks and have fluid with another therapy, I will bring them back at 6 weeks. But what I learned very quickly that these high-need patients, if you just give them one injection, dry them out, and extend right away, they may have fluid recurrences very quickly. And we saw that in TRUCKEE study also, that one injection, you're dry, and then you start extending by 2 weeks or 3 weeks, they have fluid. So one thing I do is I extend them slowly, number one.

Number two, I realize that if you load the patient in neovascular AMD at the same interval, meaning they were at 6 weeks with fluid, you give one faricimab, they're dry, I like to do a few more at the same interval to kind of really get that Ang2 inhibition activated, and then extend. And what we have seen is that with continuous treatment, you actually get better outcomes. So I'm doing it a little bit differently now; I'm not extending them right out of the gate if they're dry after one injection, but I'm also not decreasing the treatment interval compared to what they were on previously.

**Dr. Csaky:**

Well, that's very helpful. And I think as your point, you know, is that it's to me, it's very much how the patient presents, right? If they're kind of high need, lots of activity, then I think we need to be a little bit more cautious. Someone who has a perhaps a little bit more lower need, lower activity interval, responds extremely well, like Christina and I, we can perhaps extend a little bit more quickly. But I think knowing that it's all individualized is an important aspect.

Again, when we talk about fluid, I think this is where Ang2 inhibition really is – this is where the, in my opinion, across all of the trials, it's the control of fluid that I think is the real advantage to Ang2 inhibition. And I think that also helps explain the durability as well. And we saw that in TENAYA and LUCERNE, right, if we looked at the degree of ability to control intraretinal, subretinal fluid in these neovascular AMD patients, clearly, faricimab, like diabetes, was a much better drying agent and controlling fluid. So I think that's a key feature. And we're so OCT driven, and it really helps us have that confidence that we're doing something.

And of course, similarly to what we saw in YOSEMITE and RHINE, when we look at the time to when there was the absence of any fluid, intraretinal or subretinal fluid, you know, that time was also much quicker achieved with faricimab than with aflibercept. So again, it kind of speaks to this rapidity, this ability to control the fluid quickly. And again, I'm going to be really curious as we go longer and longer and longer, this impact, this better drying component that we see across all of these diseases, and quite frankly, across many, many trials, I think, is such a key feature of dual inhibition. And also it's great to also show patients that their treatment is having an impact.

So this is again, you know, what I term, not so much the high-needs patient, but the kind of more severe anatomic patient, right? And so here again is a patient who came in, was actually referred to me because the previous physician had treated with some aflibercept injections and had a poor response. And so the patient came for a second opinion. Again, I saw her. Here she is at 20/50. And when we looked at the previous, you know, kind of her history, it was clear that her response to aflibercept had been very marginal. There had been some very minimal improvement in vision, and, again, a little bit of improvement in this kind of draping subretinal fluid, but she still had this persistent pigment epithelial detachment. And you know, in my experience in the anti-VEGF era, these were real killers for me because we just in many cases could not control these vascular PEDs no matter how aggressive we wanted to be with our anti-VEGF agents. But again, in my experience, these are the cases, I call them the high-needs anatomic cases, where I think using the dual inhibition is where you can get a real wow effect. And I think these are the cases that really kind of convince me that dual inhibition has a very key role to play, especially in these kinds of cases where there's real aggressive disease. And obviously, this patient did very well, even with one injection of faricimab with an improvement in vision. You can see the PED basically is gone. And that's not an uncommon experience that I've had with faricimab.

So again, just throwing it out to the team here, you know, PEDs used to be, you know, a real bane of our kind of experience, and just curious, maybe we'll start with you, Arshad, is this something similar that you've also seen as it relates to these, what I call high-needs anatomic patients?

**Dr. Khanani:**

Yeah, I totally agree with you, Karl. The serous PED resolution is quite remarkable, and after one injection, most of them can flatten. And that's my experience in clinical practice, in naïve patients, and even switch patients. And obviously in the TRUCKEE study, we

have also seen the significant reduction in PED. So I totally agree with you. I think that is a disease activity marker, and with dual inhibition, we are seeing better outcomes with faricimab compared to VEGF-A inhibition in terms of PED flattening.

**Dr. Csaky:**

Exactly. And again, you know, it does speak a little bit to the kind of composition of the PED. You know, this is some of the data from TENAYA and LUCERNE, and you know, we do have to be a little bit aware that not every PED is the same, and there can be different aspects to the PED and their responsiveness. But I think overall, especially if there is a fibrovascular component or a vascular component, I think those patients can do much better.

And so when we look at the pooled results of TENAYA and LUCERNE in terms of the patients that had a resolution with these serous PEDs, we saw, again, a much better response as it relates to faricimab compared to aflibercept, right? And again, I think part of this has to do with the fact that if it's a pure fibrovascular where there's really very little tissue to disappear, you're not going to get quite the response. But if there is enough serous fluid within that fibrovascular PED, then you're going to get resolution.

So again, in these cases, I think we have to be aware of what's inside those PEDs. If there is a fibrovascular component, they're going to respond. But I think if there's just fibrovascular tissue, without any room for the PED to collapse onto itself, you may not see quite the wow effect. But like in this case that I showed, where clearly there was serous fluid within the fibrovascular tissue, you can see resolution of that of that component.

So I do think that it really, for the audience, be aware that we have to be a little bit more cognizant of the fact that the OCT shows us a lot of what is capable of resolution and what is still responding, which is simply not able to collapse because there's tissue there.

One other aspect of, I think, dual inhibition that we have to be aware of is also, and again, what I call these high-need anatomic cases. And this is especially in the setting of what we call SHRM, or subretinal hyperreflective material, which we know is some kind of fibrinoid material that is a precursor to fibrosis. And this is, again, something that I think needs special attention because these patients, if they're left poorly treated or undertreated, I think, have a high risk. We know that from data from CATT that they can have a high risk of going on to fibrosis. And so here's an example of a patient who comes in with, again, minimal fluid, but has a fair amount of this hyperreflective material. Vision at 20/100. You can see we began with aflibercept injections every 4 weeks trying to resolve it. Really got very poor response, and we switched right over to faricimab on this case. And you can see there was then almost dramatic resolution of the SHRM with improvement in the visual acuity.

So I think this is again a teaching case for me, that these are the types of cases now that I go right to faricimab right from the beginning because with my previous experience with aflibercept, we don't get quite the dramatic resolution. And you need that dramatic resolution to prevent fibrosis from occurring. So I think these are particularly the cases where you want to strongly consider beginning with dual inhibition.

**Dr. Khanani:**

Great case, Karl. I totally agree with you, subretinal hyperreflective material, even patients with subretinal hemorrhage, we have seen rapid resolution with minimal fibrosis. And as you alluded to earlier in this program, Ang2 inhibition can be antifibrotic. So obviously we don't have perspective data on that because it's very hard to measure that. Plus, you know, trials excluded patients with fibrosis and central hemorrhage, but I think that's something I've also seen in terms of the benefit of dual inhibition with resolution of subreflective – subretinal hyperreflective material, as well as hemorrhage without much fibrosis.

So, thank you, Christina and Karl, for a great discussion. I think to summarize our webinar today, we have seen that dual inhibition of Ang2 and VEGF really addresses the pathology in a multifactorial way in patients with neovascular AMD, DME, and RVO. And what we have seen, especially with our experience now for almost 2 years in patients with NAMD and DME, is that we see rapid improvement in anatomy in both previously treated as well as naïve patients and leading to superior anatomic outcomes compared to VEGF-A inhibition. And I think that is something that leads to greater durability with dual inhibition.

Obviously, you know, we have the new agent aflibercept 8 mg available in the trials, as Karl showed us. We have not seen better drying with 8-mg aflibercept compared to 2-mg in the PULSAR and PHOTON studies. And of course, we are evaluating now the real-world experience in terms of switching patients who have persistent disease on faricimab or other agents to aflibercept 8 mg to see if we can see better anatomic outcomes. And I think safety is important for all of us. That's why TRUCKEE study was designed. I've personally not seen a difference in safety in the real-world setting; the rates appear to be comparable to other agents. And of course, we did not see that in clinical trials in both YOSEMITE/RHINE or TENAYA/LUCERNE.

So that's my conclusion. Christina and Karl, any closing thoughts from you? We'll start with you, Christina.

**Dr. Weng:**

No. Thanks. It's always fun to be together with you and Karl. I thought they were great cases, and I hope it lends the viewer some examples when they think of their next patient for the treatment decisions that they're going to need to make. I mean, we have so many different agents to choose from. It's really wonderful because every patient is different, and every condition is different. So just very exciting for our field to have all of these new agents and more in the pipeline.

**Dr. Csaky:**

Yes, and I would just say that, you know, this is exactly if we look at where we are, I think we're just at the beginning, as I said earlier, of a new era of really understanding the full potential of dual inhibition and what patients will benefit most from this type of approach is where we'll be in the next several years. So it's going to be a very exciting time, but be aware that there's clearly patients in whom faricimab dual inhibition really should be seriously considered.

**Dr. Khanani:**

I agree with both of you. And I think it's very exciting times because we are doing in the retina space what oncology and other fields have done already, that we are going from one target to multiple targets. And I am really excited that I get to talk to both of you about this. So thank you to both of you for being here and bringing your expert opinions and great cases. I also want to thank the audience for tuning into this webinar. For additional opportunities for CME credits, please visit the Paradigm course catalog on the website listed here. Thank you. And thank you again, Christina and Karl.

**Dr. Weng:**

Thanks for having us, Arshad.

**Dr. Csaky:**

Thank you, Arshad. Fantastic job.

**Announcer:**

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