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MedEd TALKS Podcast

Novel Mechanisms Beyond Anti-VEGF for Treatment of nAMD

Speaker: You are now listening to MedEdTalks Ophthalmology, a Vindico Medical Education production. The following Podcast Series is titled *Sight-saving Therapeutics for the Treatment of Neovascular Age-Related Macular Degeneration*, and is supported by an educational grant from Allergan, Inc. To earn CME credits, login to MedEdTalks.com and search neurovascular age-related macular degeneration, or click the link in the notes section of this podcast to go directly to the activity, take the test, and complete the evaluation. Before beginning this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives. Now, here is your host, Dr. Arshad Khanani.

Arshad Khanani: Hello, and welcome to this podcast. I am Arshad Khanani, with Sierra Eye Associates. Today, I am joined by Dr. Peter Kaiser, the Chaney Family Endowed Chair in Ophthalmology Research and Professor of Ophthalmology at the Cole Eye Institute, Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio. Welcome, Peter.

Peter Kaiser: Hi, Arshad. Thanks for having me on this podcast.

Arshad Khanani: Thanks for joining us, Peter. And in this podcast, we are going to discuss novel mechanisms of emerging therapies for the treatment of neovascular age-related macular degeneration. So Peter, tell me, looking at the treatment landscape for emerging therapies, what are you really excited about, and why?

Peter Kaiser: Well, first of all, anti-VEGF, the gold standard, it works tremendously well. It has caused a revolution in our treatment of neovascular macular degeneration. But unfortunately, there is sort of a ceiling effect. First of all, all the drugs seem to get about the same level of visual acuity. We do not seem to be able to get beyond that. And they require a lot of injections. Every study we have ever done that shows reduced number of injections leads to reduced acuity.

So, because of that, we are looking for other targets, and other ways to deliver anti-VEGF that allow us to treat either with longer durability, or hopefully, by actually causing the CMV to regress because really, when we think about it, anti-VEGF doesn't cause CMV regression. Not one study has ever showed CMV disappearing from any anti-VEGF phase 3 study. And so, we want to look at other pathways that may hopefully actually cure disease, as opposed to treat the symptom of the disease, which is the leakage.

Arshad Khanani: So, I think that is a very good point you made, right? Anti-VEGF has revolutionized what we do. But I think there is still a need for more durable agents or better efficacy, as you said. So, we really want to extend the treatment interval, but we also would love to see better visual acuity, as you said. So, tell me, when you are really closely involved with the angiopoietin (Ang)-2 tyrosine-protein kinase (Tie)2 pathway. You are involved with the DARPins and other novel molecules. So, tell me first about Ang-2 Tie2 pathway and

faricimab and how that fits into your argument about durability, as well as maybe better efficacy in patients with retinal vascular diseases, especially neovascular AMD.

Peter Kaiser: Normally, when we think of something, we try to block it because it is bad, but the Tie2 pathway is interesting because when Tie2 is activated, it limits vascular permeability, it blocks neovascularization, and reduces inflammation. It is basically the good state. We want Tie2 activated, and the way it is activated is with angiopoietin-1. This stabilizes the vasculature that improves vascular survival.

In contrast, angiopoietin-2 is actually a weak agonist, but what it does is it prevents angiopoietin-1 from activating Tie2, so in a way, it activates Tie2 and when it does this, it destabilizes the vasculature, leads to endothelial cell activation, leads to leakage, inflammation, apoptosis, et cetera. So, since angiopoietin-2 causes all of this, a lot of companies have said, well why don't we block angiopoietin-2 because it is a totally different pathway from VEGF.

Now, the two actually pretty closely interact between VEGF and Tie2, but if you could block the angiopoietin-2, that may improve our outcomes. And what the molecule faricimab is looking at is blocking angiopoietin-2 as well as VEGF using the same molecule, thereby leading hopefully to better outcomes. In the early phase 2 studies, we did have a slight improvement in vision over anti-VEGF, at least to diabetes (not macular degeneration), and a longer durability. So hopefully, the phase 3, which are fully enrolled at this point, will show a similar result, and will have another treatment for this devastating problem.

Arshad Khanani: So, I think you made a really good point, that VEGF Ang/Tie pathways are kind of interconnected. So, I think the VEGF is still the primary driver of neovascularization and leakage but blocking Ang-2 may lead to better vasculature or quiescent vasculature, less inflammation, stability. So, I think your point about going to a normal state makes perfect sense, that if you can get the vasculature to a normal state, I think that may show some benefit. And we will see how the phase 3 data pans out for DME and also for neovascular AMD. Talking about unique molecules, DARPin obviously is a newer class of molecules that block VEGF-A. So, tell us a little bit about DARPins and what are your thoughts on it.

Peter Kaiser: So, DARPin platform is based on this idea of designed ankyrin repeat proteins. So, these are proteins that kind of are stacked together, and very tightly binds whatever cytokine you are trying to block, in this case VEGF-A. So, because of that, the molecule is relatively small, very similar to say, brolucizumab size. And so, the company decided that to improve the half-life of the drug, they pegylated it, and this increases the size of the molecule, thereby improving the half-life of the molecule. And in fact, when you look at abicipar itself, the binding affinity is one of the tightest binding affinities of any of our anti-VEGF drugs and that equates to longer durability.

And in fact, in the phase 3 studies, the drug showed that it can actually be delivered every 12 weeks versus ranibizumab delivered every month.

Arshad Khanani: So, I think that is interesting that the unique characteristics of the molecule, you have to look at binding affinity, you have to look at molar dosing, and then you have to look at half-life, and I think you have to balance all those out to get a more durable molecule. And I think abicipar clearly has most of those characteristics, and we will talk about the phase 3 data in a later podcast. But I think to summarize, even though it blocks VEGF-A,

it's a new class of proteins, DARPins are, and we'll see how that fits into our treatment paradigm.

Now, moving on to tyrosine kinase inhibitors, GB-102 is under investigation. We have early data, and they are currently recruiting for their ALTISSIMO study. Can you describe for our audience, what tyrosine kinase inhibitors do and how they function and what is the science behind GB-102?

Peter Kaiser: So, all the receptors that we think are involved in macular degeneration, not all, but the majority, for instance, VEGF receptors 1, 2 and 3, the PDGF receptor, as well as even the type 2 receptor. These are all tyrosine kinase receptors. In other words, once they are activated, it leads to phosphorylation cascade, which is based on the tyrosine kinase enzymes.

And so, in oncology, there has been a lot of excitement about targeting certain aspects of the tyrosine kinase cascade. It is important to understand that when you say a tyrosine kinase inhibitor, that is a catch-all term, because there's many different areas within the cascade that you could possibly block.

And most of the ophthalmic companies have taken off-the-shelf tyrosine kinase inhibitors and put them into certain platforms. So, some companies have put them into eyedrops, some have done it systemically, some have put it into sustained-release platforms. So, GB-102 and OTX-TKI are two different TKIs that are put into a polymer form and injected in the eye, and thereby have a long durability of activity.

But there are 2 questions anytime you talk about a tyrosine kinase inhibitor because the 1 question is, how tightly does it bind the tyrosine kinase it is inhibiting, and how involved is that tyrosine kinase in the permeability and angiogenesis cascade of neovascular macular degeneration? So, you really have to ask yourself those 2 questions.

Now, unfortunately, to date, there has been no tyrosine kinase inhibitor that has been successful in neovascular macular degeneration, and that is unfortunate because we have had several different eyedrops fail. We have had several different systemic tyrosine kinase inhibitors fail. But the GB-102 product, there was an early study and it looks to at least have an extended durability. As I said, this is a polymer injection that forms a depot and slowly reabsorbs over time. It is PLGA, just like the dexamethasone implant. So, it basically breaks down to water, lactic acid, and glycolic acid and disappears completely, totally bioerodible.

But each of these have different tyrosine kinase inhibitors. Clearside has a tyrosine kinase inhibitor that they are injecting in a suprachoroidal space. So, tyrosine kinase inhibitors are very exciting because theoretically, they could block multiple different receptor activations. But I temper that enthusiasm; we have to see if any of these actually work.

Arshad Khanani: Right, exactly. Sometimes the science is making sense, but are we getting the efficacy that we need? And especially VEGF-A blockade, with agents we have, they raise the bar so high in terms of efficacy and safety that they really have to come very close to that. And especially safety, as you know, so that's why I am excited about the pathway. But

again, just like you, I want to see data to see how we can take these molecules to help our patients in clinic.

Moving on to conbercept, and I know you and I are both involved in the trials, when people think about conbercept, they just think about aflibercept. They think that it is just similar to aflibercept. Can you tell us why conbercept is different than aflibercept and why do you think it can fit in our treatment paradigm to help our patients?

Peter Kaiser: Yes. So, it actually is relatively similar to aflibercept, so you would not be incorrect thinking that. The difference is, it is a VEGF trap molecule and unlike aflibercept, it adds VEGF receptor to domain 4. And that additional domain that is on conbercept does a few things. First of all, it makes the binding to VEGF much tighter. It reduces the dissociation rate, so it binds tighter.

The other thing that it does is it actually changes the isoelectric point. So, by changing the isoelectric point, it actually prolongs the clearance time. So, if you bind tighter, and you have longer clearance, theoretically, we could have a longer durability, but bind the same molecules as aflibercept. So, unlike say the DARPin, abicipar, this binds VEGF-A, -B, -C, and placental growth factor. And maybe that is beneficial, maybe it is not. Maybe we only need to block VEGF-A, but just like aflibercept that binds more things. And in the phase 3 PANDA Study, they are actually looking at this drug every 3 months, versus aflibercept every 2 months, so the results of that study will be out sometime next year.

Arshad Khanani: I think it is exciting that if we can have similar efficacy in BCVA gains and similar safety, and if we can have better durability because of the slight differences in the molecular design, I think that may be very beneficial for our patients.

Peter Kaiser: Well, the selling point of getting this study is the longer durability, but unlike many phase 3 studies, we had over 500,000 injections in China. This drug is approved in China already, so we know sort of the safety of this drug, which we don't really see for a lot of the new drugs we have out there in phase 2 and 3.

Arshad Khanani: So, I think that is a very good point that the safety and efficacy has been well established. The question is how much better, in terms of durability, the molecule is compared to aflibercept. So, before we wrap up, just a quick comment about KSI-301. What are your thoughts on the molecule and some of the trial data?

Peter Kaiser: So, KSI-301 is an interesting molecule. First of all, as I told you before, large molecules last longer, and this is the largest molecule we have. It is a huge polymer, where they put the complimentary binding region (CDR) for ranibizumab into immunoglobulin G (IgG), and the size of this thing is monstrous, like 950 KD. And because of that, theoretically, it could last almost 4 to 6 months.

And so, in the early studies, we saw this long durability. It is a VEGF-A inhibitor, because it has ranibizumab CDR. But the hope is that we could actually have this drug work for 6 or even longer months with a single intravitreal injection. So, same efficacy hopefully as ranibizumab, longer durability. But again, this is in early phase 2/3 testing. So we will have to wait to see if there are any inflammation issues, etc that we're seeing in some of these newer anti-VEGF agents.

Arshad Khanani: Yeah, that is what I was going to say, is that a big polymer in the eye, when you think about it, you may well expect inflammation. And we are involved in the trial and the safety profile so far obviously has been pretty clean, and I think it does offer another option for our patients to have a more durable treatment.

So, last question for you. So, we discussed faricimab, GB-102, KSI-301, conbercept, DARPins, so tell me when you're looking at these treatments, what are you looking for, in terms of the pathway to approval and how are you going to integrate these treatments in your current paradigm? Especially when you have really safe agents in ranibizumab and aflibercept, and obviously brolucizumab is also an option, and we have discussed some of the rare adverse events with it.

Peter Kaiser: Well, I think you hit the nail on the head there, which is that, obviously, we look at the efficacy in the phase 3 clinical studies. But I think now as retina specialists, we are much more targeted at the safety. This is something we just kind of assumed that all these drugs are safe if it got past the FDA. And we are finding there are some issues; IOI, intraocular inflammation, is certainly an issue. We are seeing some of this in very severe form with some of these newer molecules, so we are going to be looking very closely for that with the newer drugs to make sure we do not see that.

But to me, the exciting thing is, can we move the bar forward some? And faricimab, of all the drugs we have talked about to date, is one that actually is moving the bar, I hope, forward. At least the DME studies showed extra efficacy, a significant improvement over ranibizumab alone. So, I hope we see that in the macular degeneration studies, that by adding another pathway that we are blocking, we can move the bar forward for our patients.

Arshad Khanani: That is excellent, Peter. Thank you for joining me in discussing this topic, and thank you all for joining us for this podcast.