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On the Horizon: Achieving Durable VEGF Suppression in nAMD and DME

Announcer:
Welcome to CME on ReachMD. This activity, entitled “On the Horizon: Achieving Durable VEGF Suppression in nAMD and DME” is provided by PROVA EDUCATION.

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Dr. Do:
One of the biggest challenges with intravitreal anti-VEGF therapy is the continued need for high-frequency treatment. This can be a burden for both patients and their families, leading to missed appointments and lower visual acuity outcomes. Fortunately, new treatments are on the horizon in both neovascular age-related macular degeneration [nAMD] and diabetic macular edema [DME]. What we are looking for today is medicines to reduce the treatment burden, while also improving vision and providing a safe therapy for our patients. What is the latest evidence that shows these new medicines may be promising?

This is CME on ReachMD. I’m Dr. Diana Do, and joining me today are my friends and colleagues, Drs. Nancy Holekamp and Carl Regillo. Welcome.

Dr. Holekamp:
Thank you for having me, Diana. It’s great to be here.

Dr. Regillo:
Thanks, Diana. Pleasure to be here, too.

Dr. Do:
Let’s get down to this exciting discussion. We’re going to be covering several topics during today’s presentation, including mechanisms of emerging interventions, supporting clinical evidence in neovascular age-related macular degeneration, gene therapies and other agents in late-stage development, recent clinical trial data in diabetic macular edema, and applications to your clinical practice.

Nancy, let’s start with you. There are several strategies that are being evaluated for patients with wet AMD and diabetic macular edema. Can you tell us a little bit about faricimab, which is in late-stage development? Please also tell us about your insights on brolucizumab, which is being evaluated for diabetic macular edema. Nancy?

Dr. Holekamp:
So faricimab is really a unique molecule. It is a bispecific antibody, targeting both VEGF-A and Ang-2. And the thought is by targeting Ang-2, you can stabilize vessels, suppress the pathologic angiogenesis, and thereby provide greater durability and longer treatment intervals.

So brolucizumab is a unique anti-VEGF in that it’s very, very small. It’s a single-chain antibody fragment. And the thought is by being so small, you can really pack a lot into a syringe, so the treatment dose is a very, very high molar dose. Again, the thought being that increasing the molar dose increases durability and decreases the treatment burden.

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Dr. Do:
Thank you, Nancy. Those are very exciting strategies.

Carl, tell us about the port delivery system, which is also in late-stage development.

Dr. Regillo:
The port delivery system is truly sustained delivery of anti-VEGF therapy. It's a scleral-based, intraocular reservoir device, designed to deliver a concentrated version of ranibizumab into the vitreous cavity. It's a device that's inserted in the OR, and then refilled in the office setting.

We've actually created a brief 3D animation to visualize how these new mechanisms work and how they compare to the first-generation VEGF inhibitors. So let's take a look.

[VIDEO PLAYS: Therapies targeting VEGF-A have become the gold standard of care to combat choroidal and retinal neovascularization and leakage. A new generation of strategies is emerging with the goal of better drying and greater durability. Brolucizumab is a single-chain antibody fragment binding VEGF-A to block angiogenic signaling.[Tadayoni2020] Faricimab is a bi-specific antibody targeting both VEGF-A and angiopoietin-2 or Ang-2.[Regula2016] In diseased vessels, Ang-2 and VEGF synergistically drive vascular instability.[Regula2016] Ang-2 competitively binds Tie-2 receptors on endothelial cells to prevent quiescence driven by Ang-1.[Regula2016] Binding of Ang-2 by faricimab enables Ang-1/Tie-2 signaling. The combined inhibition of Ang-2 and VEGF-A suppresses pathologic angiogenesis and improves vessel stability. Finally, the port delivery system is a refillable implant that provides concentrated ranibizumab for continuous VEGF suppression via passive diffusion.[Campochiaro2019] Together, these new strategies offer improved treatment durability for patients with neovascular age-related macular degeneration and diabetic macular edema.]

Dr. Do:
That's also very exciting. Now, let's look at the data that shows why these late-stage molecules provide evidence for potential efficacy and safety in wet AMD.

Nancy, can you walk us through some of the key data for faricimab in neovascular AMD?

Dr. Holekamp:
So, Diana, TENAYA and LUCERNE are the 2 identical clinical trials of faricimab. The comparator is aflibercept with 3 loading doses, followed by Q2-month dosing. But faricimab actually had 4 loading doses, and then had a disease activity assessment, where patients were parceled out to being dosed every 8 weeks, every 12 weeks, or even every 16 weeks. But once you were on that dosing regimen, you never dropped down, you never changed, and you were on that dosing regimen through the first year of the study. Now we don't have Year 2 data, and that will become more of a treat-and-extend type paradigm.

So when we look at the visual acuity results, and we're looking at the mean change in best corrected visual acuity [BCVA] over the first year, we see that the lines for both faricimab and aflibercept are essentially on top of each other. And what that means is that faricimab was non-inferior to aflibercept, as regards visual acuity gains. An important secondary endpoint is the mean change in central subfield thickness on an OCT. And when we look at that data, from both TENAYA and LUCERNE, again we see that the lines for faricimab and aflibercept are almost identical. And in the matched phase of the early stage of the first year of this clinical trial, we see maybe perhaps even a slight advantage to faricimab for better drying. So that's provocative and very encouraging.

But we're really here to talk about increasing durability of treatment. And it's very exciting that TENAYA and LUCERNE had essentially similar outcomes, where 45% of patients were dosed at Q16 weeks through the first year of treatment, and 34% to 33% of patients in each study were dosed at Q12 weeks through the first year of treatments. And if we add those together, we see that between 75% and 80% of patients in both studies were being dosed at either Q12 weeks or Q16 weeks, and I don't think we've seen that before with any of our first-generation anti-VEGFs.

Now, what people are most interested in now is safety, and the safety profile looked very, very good for faricimab. We saw no new safety signals, and in fact there was a deep dive into iritis, uveitis, vitritis, even retinal vasculitis, and those complications were comparable to the comparator which is aflibercept. And that is to say that all of those occurred in a very low percentage of eyes, a fraction of 1% throughout both studies, across all arms. So what we know from TENAYA and LUCERNE is that faricimab met the primary endpoint of non-inferiority regarding visual acuity outcomes, and when we look at durability, there was impressive data, with about between 75% and 80% of patients being dosed at either Q12 or Q16 weeks, and faricimab seems to be safe as far as phase 3 clinical trials can tell us. And there were no cases of vasculitis or occlusive retinitis. Now, the second-year data is going to be very important for looking at continued, extended durability, and then both TENAYA and LUCERNE will roll over into a long-term extension study, called AVONELLE-X. So there is a lot of data yet to come with faricimab in wet AMD.

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Dr. Do:
That's very exciting and compelling data, especially the fact about the durability of faricimab.

Speaking of reducing the treatment burden, Carl, can you share with us the pivotal phase 3 data on the port delivery system in wet AMD?

Dr. Regillo:
Sure, Diana. This was a successful program. The bottom line is the port delivery system, at phase 3 testing, called the ARCHWAY study, met its primary endpoint in terms of comparing mean change in BCVA from baseline to the control group, being non-inferior and actually equivalent to gold standard monthly ranibizumab injections. So the study was a 2-arm study. Patients either got the port delivery system implanted or monthly injections. And the primary endpoint was averaged weeks 36 to 40, again changing from baseline in mean BCVA. What's unique about this study and this approach is this is effectively in the maintenance phase of therapy. Patients were previously treated – recently diagnosed, but had a mean of about 5 treatments, so they had already been through the induction and probably all the vision gain, for the most part, that they were going to get, at least on average. In fact, at baseline, they were 20/32 in each arm, and at the primary endpoint, both arms were 20/32 – exactly the same visual acuity from beginning to end. And excellent exudative control was seen in both arms, again, essentially equivalent out through the primary endpoint. And we now have data out through about 18 months, or 72 weeks, and it continues to show the port delivery system stacking up very well to monthly injections, both in terms of acuity and exudative control. And in the study, it was possible for patients in the device arm to get supplemental injections a month or 2 after the fixed refill, which occurred at every 6 months. And very few patients – less than 2% in the first refill cycle, and about 5% in the second refill cycle – got supplemental injections in the PDS treatment arm. So PDS held up very well in terms of disease control, and so that's really encouraging. It performed very, very well.

What about adverse events? And this is unique. It's a surgery; it's a device; it's not going to look the same as what we're accustomed to in clinical trials and in practice with intravitreal injections. So when we look at adverse events specifically attributable to or potentially associated with the device, we've had some issues with conjunctiva retraction and erosion coming in at around 4, 4.5%. And endophthalmitis – and this is per patient rate of endophthalmitis – was 1.6%. The good news is that these events occurred mostly in the first year, or up to the primary endpoint of 40 weeks, and very few new adverse events associated with the device occurred thereafter, now that we have longer term follow-up to 18 months. And as you get along in the follow-up, we're seeing now events or problems like a case of endophthalmitis in the intravitreal injection arm, too. So the differences in adverse events between the device arm and the injection arm is starting to lessen a little bit, so it's looking more favorable. A few other notable adverse events – there's been some device dislocations. That has to be fixed surgically. And in general, the vitreous hemorrhage issue that we saw early on in the phase 2 study is kept nice and low in this study. When you look at, again, out through 18 months, we have a vitreous hemorrhage rate of about 6% in the device arm, and actually, it's 3.6% in the injection arm. So both arms had some hemorrhages. They were mainly mild, and none of them needed any intervention.

So the safety profile is looking quite good overall, again, considering that it's a surgery and it's a device in the eye, and it's not going to look exactly the same as an injection. It's just not possible, but it is looking good. And we've learned a lot about surgical techniques and how to mitigate these types of problems, especially the conjunctival issues, which is a setup for infection, so we want to try to do our best to minimize these types of problems. And if you want to learn more about PDS surgical techniques, what we've learned, and how to mitigate the problems, please visit EyeHealthAcademy.org, and that's eye, e-y-e, EyeHealthAcademy.org.

Dr. Do:
For those just tuning in, this is CME on ReachMD. I'm Dr. Diana Do, and joining me today are my 2 close friends and colleagues, Drs. Nancy Holekamp and Carl Regillo. We're exploring new strategies in the treatment of retinal neovascular diseases and are looking at medicines in late-stage development for the treatment of wet age-related macular degeneration, and diabetic macular edema.

There are other medicines in late-stage development for retinal vascular diseases. Let's talk about KSI-301, a novel anti-VEGF antibody biopolymer conjugate.

Nancy, can you share some highlights for us?

Dr. Holekamp:
Sure. So KSI-301, I call it a designer drug, maybe anti-VEGF 2.0, and it's been tested in a phase 1B open-label study with about 50 patients with wet macular degeneration. And when you kind of summarize that phase 1B experience in wet AMD, the durability was pretty impressive. After 3 loading doses for the rest of the year, on average, patients needed 2, for a total of 5 mean injections in Year 1. So that's pretty exciting for an anti-VEGF injection. If you look across the entire phase 1B wet macular degeneration experience, about 66% of patients could go 6 months without needing rescue injections or additional injections. So this is still early stage. In fact, the pivotal clinical trial in wet AMD is just about to take off. It's called the DAZZLE study. They're going to look at 550 treatment-naïve wet

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AMD patients. They're going to randomize against aflibercept dose as the on-label standard of care. It's going to take place in the US and Europe, and KSI-301 is going to be very bold. It's going to look at dosing every 12, 16, and even 20 weeks, based on prespecified disease activity assessment.

So, Diana, I think that this is really an interesting molecule, and I think we'll all watch and wait and see what this DAZZLE pivotal clinical trial will show us.

Dr. Do:
Thank you, Nancy. It sounds very promising.

Carl, let's talk about OPT-302, which is a new intravitreal agent that blocks VEGF-C and VEGF-D, which we had not attacked before. Can you give us some highlights on this new molecule?

Dr. Regillo:
Sure. You know, studies have shown that VEGF-C and -D is upregulated when you block VEGF-A, which is what we've been doing to treat wet AMD/DME to date. So the rationale here is that blocking C and D in addition to A might give us better results, in particular, vision. And then that's exactly what the Phase 2B study showed for OPT-302. So it's not a stand-alone drug. It's a fusion protein meant to be injected in combination with anti-VEGF-A therapy. So in this study, it was ranibizumab monthly as the control arm, versus 2 doses of OPT-302. And indeed, it showed a dose response in terms of better vision gains, up through the endpoint in the study at week 24.

And OPT-302 is now moving along into phase 3 testing – the ShORe and COAST studies – and it's being used in combination with ranibizumab and aflibercept. So within a couple years, we'll know a little bit more about this combination approach.

Dr. Do:
Thanks, Carl.

There are also gene therapies in development, which are very exciting. Nancy, can you tell us a little bit about RGX-314?

Dr. Holekamp:
Sure. I'm actually very excited about gene therapy, and this is the first retina gene therapy that has really shown a lot of promise. Carl will talk about the second one, but we'll start with RGX-314. It's an AAV8 vector, with an anti-VEGF fab gene. So what does that mean? It means that we're using gene therapy to transfect cells under the retina and create biofactories that produce something very similar to ranibizumab. So this drug – this gene therapy – has to be injected into either the subretinal space with vitrectomy surgery, or into the suprachoroidal space with a specialized needle, a suprachoroidal injector. And so far, it's been tested in a phase 1/2 study, so very early. It's been tested mostly with the vitrectomy and subretinal delivery approach, but in these early-phase clinical trials, particularly in the later cohorts, where we're injecting almost a billion viral genomes into the eye, we see great suppression of activity in wet macular degeneration, and we see durability.

It's important to note that these eyes being given gene therapy in these early-phase clinical trials are eyes with a very, very high treatment burden – lots and lots of injections. And then we see after the gene therapy procedure, that they have far fewer injections. In fact, in Cohort 5 for this early-phase clinical trial for RGX-314, out of the 11 patients treated, only 4 required rescue injections.

So I think to say that gene therapy is one and done might be a bit of an overstatement, but if we're looking at an approach that has really long durability, that can certainly decrease this treatment burden for our patients, I think gene therapy is exciting, and I think RGX-314 is on a good path to see if their product can do it. In fact, they have planned a couple of subretinal injection clinical trials. It's a pivotal trial for wet AMD. It's called ATMOSPHERE. They also have a phase 2 clinical trial for the suprachoroidal injection of their gene therapy product called AAVIATE. So I think that this a very exciting area for wet AMD. Again, in early stages right now, but stay tuned.

Dr. Do:
Another gene therapy that's being evaluated in clinical trials is ADVM-022. Carl, can you give us a few highlights on this drug mechanism?

Dr. Regillo:
Sure, this is the other gene therapy approach to wet AMD and also starting trials for DR [diabetic retinopathy] and DME, too. And the big difference here, this is an intravitreal injection, and it's used using a modified AAV, with a 7m8 capsid designed to encode a gene to express aflibercept. So here, we're making aflibercept after an intravitreal injection of the viral vector. In that OPTIC phase 1, it looked really promising. We've got now high-dose and low-dose cohorts here out through a year and a half, 2 years of follow-up, and the high-dose in particular is looking very, very good in terms of exudative control. In fact, Cohort 1 the first high-dose cohort – 6 out of 6 patients have been supplemental injection-free. So that was truly one and done. And Cohort 4 is the other high-dose cohort, also looking very good. And even the lower-dose cohorts are controlling exudation with a much reduced need for any supplemental or

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rescue injections of anti-VEGF in the study thus far. So looking very good.

When you inject a viral vector intravitreally there can be inflammation. In fact, we're seeing inflammation relatively frequently. It seems to be relatively well controlled with 1, 2, 3 drops of steroids a day, and not all patients necessarily need the steroids ongoing to suppress the inflammation, but we're learning a lot in terms of who needs treatment and when and how to control this inflammation, which is something that, going forward, we'll need to learn a lot more about, and as this moves on to more advanced phases.

Dr. Do:
Now let's move to diabetic macular edema, another area of unmet need. Nancy, can you tell us about the new data on brolucizumab in diabetic macular edema, and if there are any safety updates?

Dr. Holekamp:
Sure, and you're right, this is brand-new data. The phase 3 clinical trials in diabetic macular edema were called KITE and KESTREL. And it was a study designed for up to 52 weeks, and when we think about reducing treatment burden, the study design is actually significant, because for the first time, brolucizumab was being loaded every 6 weeks, as opposed to every 4 weeks. And then there was a disease activity assessment, and then patients were followed through the first year of treatment. And significantly, KITE and KESTREL met their primary endpoint, that brolucizumab in the 6-mg dose was non-inferior to aflibercept in change from baseline in best corrected visual acuity at week 52. And, there were significant improvements in the central subfield thickness, and in fact, even in KITE, there looked to be maybe, perhaps, a slight advantage for brolucizumab anatomically in the one study.

But as you mentioned, Diana, we're very keen on looking at the safety profile of this small molecule, this brolucizumab, and when we looked at the intraocular inflammation rate in the 3-mg arm of brolucizumab in the KESTREL study, it was 4.7%. And of course, that mirrors or echoes what we saw in HAWK and HARRIER, which led to post-marketing, widespread alarms of patients experiencing not only severe intraocular inflammation, but retinal vasculitis and retinal vascular occlusion. So while we were all very pleased to see the great efficacy data, we were disheartened to see that the safety profile from HAWK and HARRIER seemed to be repeated, at least in the KESTREL study.

Dr. Do:
Thanks for that update.

Carl, what about faricimab in diabetic macular edema? I know the phase 3 clinical trials were also completed.

Dr. Regillo:
Yeah, and also very successful. It's the YOSEMITE and RHINE phase 3 studies for faricimab in the use of treating DME. And bottom line is it met the primary endpoint in terms of mean change in BCVA from baseline to the primary endpoint of approximately weeks 52. It's a 3-arm study. The control group – one of the arms – was aflibercept dosed every 8 weeks on label after the load. And then 2 faricimab arms, also fixed every 8 weeks, so very similar. And then there was one faricimab arm that was variable dosing, or individualized dosing, called "personalized treatment interval." And that allowed for dosing anywhere from 4 up to 16 weeks and so that gave us a sense for durability.

What did it show? Of course, it met the primary endpoint, as I mentioned, and BCVA change from baseline was essentially the same for all 3 arms in both studies. And looking at control of exudation by OCT, there was definitely some results here that favored faricimab in terms of better reduction in DME. The central subfield thickness change from baseline, on average, was a bit better in the 2 faricimab arms of both studies, and even the proportion of patients that had complete resolution of DME favored faricimab. Again, both arms, compared to aflibercept. So that's very exciting, and from a durability standpoint, also, the good news here, just like in wet AMD, it looks to be a drug that's more durable than the drugs we have been using. In the faricimab PTI, or individualized dosing arm – it's sort of like a treat-and-extend arm – patients were able to be dosed 12 weeks or more 72% of the time, combined for the 2 studies, and even up to 16 weeks in 52% of the patients. That's really encouraging for durability and, as Nancy mentioned before, in wet AMD, the drug was really well tolerated, with very low rates of intraocular inflammation and nothing really here that stood out as a concern.

Dr. Do:
The port delivery system is also in late-stage pivotal trials for diabetic macular edema and diabetic retinopathy. It'll be exciting to see those results coming up in the next few years.

In our last few minutes, I wanted to transition to clinical practice and how we'll be using these late-stage molecules in development. I'd like to ask you, Nancy, how will you be using, let's say, faricimab, brolucizumab, the port delivery system, and other drugs in your clinical practice?

Dr. Holekamp:

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Well, until the safety profile improves with brolucizumab, I think it's a third-line agent, for sure. But I do see using faricimab because the results from these 4 clinical trials are very compelling, and I can see using it as a first-line agent not only for new wet AMD patients, but also perhaps switching some patients, where I'm looking for increased durability. But when we get to the port delivery system, as Carl mentioned, it's a maintenance, long-term therapy, and in the ARCHWAY clinical trial, patients had anti-VEGF injections, so I'll probably be taking my high-need anti-VEGF patients and trying to convert them over to the port delivery system.

Dr. Do:
Great. Carl, what are your thoughts? What would you use first line, and how would you position, let's say, the port delivery system in your clinical practice?

Dr. Regillo:
I agree with what Nancy said. I think we're going to get great utilization out of faricimab, and to some degree the port delivery system, too, moving forward. I think we're really going to see a lot of utilization of anything that lasts longer in our patients that are getting treatment that need injections very frequently because they're going to be most motivated to want to come to the office less and extend their treatment interval. So faricimab is very attractive in that way, and even the port delivery system.

Dr. Do:
Great. I think all of those insights are very valuable, and we can't forget that there'll be other drugs in the future, too. Who knows, maybe KSI-301 or OPT-302. So hopefully, as physicians, we'll have lots of good choices for our patients.

I'd like to thank all of our listeners today for joining us at this lively discussion. I'd also like to acknowledge and thank my friends, Drs. Nancy Holekamp and Carl Regillo, for their expertise and insights. It was a pleasure speaking with you both.

Dr. Holekamp:
Well, thanks for having me today.

Dr. Regillo:
Likewise with me. Thanks, I really enjoyed it.

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VIDEO REFERENCES:
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