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https://reachmd.com/programs/cme/treating-outside-the-box-new-pathways-to-retinal-vascular-stability/56620/

Released: 08/24/2026
Valid until: 08/24/2027
Time needed to complete: 60 minutes

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Treating Outside the Box: New Pathways to Retinal Vascular Stability

Chapter 1: Welcome

Dr. Rishi Singh:
So this program is called *Treating Outside the Box: New Pathways for Retinovascular Stability.* It's a pleasure to kind of bring you some avant-garde discussions around how we're treating vascular stability and looking at our biomarkers and these disease states. We'll talk about various biomarkers. We'll talk about new therapeutic options, which are coming online. It's an exciting place.

We were back here almost 20 years ago. I was a retina fellow, and the buzz was all on the anti-VEGF presentations at the time. We're back in the same city 20 years later, and there's actually a new buzz forming for new drugs that are coming out, and we're excited to kind of talk about them today.

I'm Rishi Singh. I'm the chair of ophthalmology at Mass Eye in Boston, Mass. I'm joined by Ferhina Ali. She's [an] assistant professor at New York Medical College, and she's a retina specialist in Westchester, New York. And we're also with Dr. Barry Kuppermann. He's chair of the Department of Ophthalmology at the Gavin Herbert Eye Institute at the University of California, Irvine. So thank you both for joining. And they're going to be taking over parts of this program so that we can all learn from them.

Here are faculty disclosures for the program today, and here are staff disclosures. Evolve is the CME supplier for this program. It has full policies in place, and this is a program that's supported by Merck Sharp & Dohme LLC.

So here are the learning objectives for today's program. We're going to apply targeted team-based strategies to reduce missed visits, treatment interruptions, and preventable undertreatment in DME and neovascular AMD. We all know this is a team sport. Obviously, retina specialists are only one part of that team. We have to have other people call these patients, make sure they come to their appointments, and we'll talk about some of the complexities around that and what the data and the community has shown. We'll identify patients with anti-VEGF refractatory diseases. We'll talk about some of those biomarkers that may improve vascular stability and talk about emerging therapeutic options. And we'll also discuss some cases, which will help to discuss what we do with nonresponders in our population. And this is one of the things where I know that a lot of us have always struggled with these nonresponders. We think we have lots of definitions on them. We'll talk about what those definitions are and how we apply them to practice.

So with that, I'm going to turn over to Dr. Barry Kuppermann. He's going to talk about undertreatment and consequences in the real world.

Chapter 2: Undertreatment and Its Consequences in the Real World

Dr. Barry Kuppermann:
Alright. Again, a pleasure to be here and looking forward to having a nice discussion as well.

So, again, treatment burden remains a significant unmet need in neovascular AMD, and we know that a significant percentage of patients, again, as you can see here, 90% of patients require injections every 1 to 3 months, and again, frequent injections are the continuous complaint. And again, visit frequency interrupts the patient's daily routines. So again, lots of days off to come into our offices, as you all know. And again, we also know that suboptimal frequency of injections contribute to declining real-world outcomes. It's an ongoing concern.

We're grateful to have the second-generation drugs. As Rishi mentioned, it was actually 21 years ago, specifically 2005. But that was, again, for those that were not there because you're too young, that was a remarkable meeting because we're in the Queen Elizabeth Hotel, and we heard for the first time bevacizumab for the treatment of neovascular AMD and the data from the MARINA study, which was ranibizumab that Phil Rosenfeld and Joan Miller presented, and we all bought our first OCT machines—that was temporal domain back then; it was the Stratus—but that launched the modern era.

And all the changes that have happened since then have been modest at best. We're grateful for them, but we're mostly doing the exact same thing that we were doing 21 years ago. Yes, a better OCT machine—spectral-domain, some have swept-source. Yes, now we have these second-generation drugs, but again, these are incremental improvements of where we are now. We're still focused on anti-VEGF.

And again, part of our concern is, is that we know that real-world vision declines due to chronic disease. It was first started with the SEVEN-UP study. That's not even referenced here. But in clinical trials, there's this nice improvement of disease stability, but the real world, over time, there's a decay of vision.

And again, what we're looking for is to maintain vision throughout the period of time, throughout the entire treatment period, meaning the rest of their lives for now.

Chapter 3: Making Adherence Actionable

Dr. Rishi Singh:
When you talk about your patients, Barry, what do you think is the most important discussion you have about treatment adherence?

Dr. Barry Kuppermann:
Again, I worry about losing patients to follow-up. Again, it depends on the disease state. Neovascular AMD, ironically, the older population tends to have better adherence. It's not unusual to have the 91-, 95-, the other day, I injected a 103-year-old. I said, "Oh, that's got to be the oldest one I'll inject." Two patients later, she was 105. It's unbelievable. They're there with daughters and granddaughters, et cetera. Tends to be a lot of women in that. I'm much more worried about the diabetics and their complex lives. They're much iller, sicker. They're 48 years old and juggling a job, 3 kids, and their healthcare issues. So I'm really worried about follow-up with them.

Okay. So again, this concern with the fall-off and patient follow-up visits, it's a big concern. How can we make adherence actionable? And again, you can see, again, we have to frame it around the disease.

And we all do this with our patients on a regular basis. We want to remind them this is a chronic disease. This is a lifelong disease. Whether it's neovascular AMD or diabetic macular edema, these are conditions, including retinal vein occlusion. I've just presented on a new molecular entity in my last presentation on the podium over there. We need to keep treating a lot of our patients for a very chronic basis. We try to extend them out to whatever degree we can, but again, we need to set expectations of patients and make sure that they get, you know, especially for example in diabetics, that first year is critical. We really try to emphasize the first year of therapy. But again, we need to set their expectations, try to exhort and encourage them to follow up.

In this current world we have with the need for frequent injections, even if they're on a treat-and-extend protocol, many of them are on that 12 weeks or less interval, so we need to get them there. And again, we want to protect what they've gained. That's the other part of it, we try to frame it and set their expectations and get their buy-in. Important part of that.

How do you make it actionable? The influences are affecting these. Disease management include lifestyle, finances, the insurance, of

course, is critical to this—sadly, it's part of our reality in the United States—social support, family demands, employer expectations, and cultural factors. And again, it varies. These will be influenced by the age of the patient. Again, diabetes, all these plays a role. And the neovascular AMD patient, many of them already at retirement age. There's several of these are still relevant, but not all.

Again, what are the barriers around? Again, dietary and fitness trends, habits—again, that's critically important. Again, the financial constraints—that's unfortunately true, but again, we try to help them, though some of the opportunities to help patients have dropped off because of some of the legal aspects of that—caregiver availability, transportation, other systemic diseases, health literacy, and language barriers. Again, that's a common thing. Again, one of our great glories of this country is the diversity we have in most parts of the country, and that means being able to adapt to different cultures and different languages.

So again, knowledge drives adherence. And again, here's an opportunity here.

There's a QR code from the AAO for more information about this. It's worth noting. I didn't realize that this one, this link here, is actually a paid service, so that one will cost you money. I don't think it charges you just dropping down the QR code but take a look at that site. But again, there's videos available to reinforce disease overviews and treatment expectations. Again, visualize disease progression over time and treatment mechanics. And again, there's handouts that are worth giving out to patients. Again, we try to keep our patients as informed as possible in this process, really to get their adherence, getting them coming back into the clinic.

And again, it's worth noting, we all think we've got good adherence, but of course it's selection bias. We're seeing the patients that keep coming back. We're forgetting about sometimes the patients that haven't come back, and suddenly they show up. It's like, "Oh yeah, Mrs. Jones. Long time no see." And I think, "Crap, I wish I'd caught her earlier."

Again, team-based workflow for sustained adherence. Reminder systems, again, as I alluded to just now, we need to do that. I mean, it's actually some places there's a medicolegal requirement up to a point, but we want to get them to be participatory, continuous in their coming in. Remind them, rapid reschedule after no-show. We all try to do that. All of us I think have adapted to that, but that's part of the service that we're committed to providing to our patients.

Caregiver activation, again, is another important aspect. Co-management touchpoints. Again, that's particularly true with our diabetic population. And again, the red flags are we need to pay attention to the things that bring us to concern. So again, all this is part of the team-based workflow for sustained adherence.

Chapter 4: Anti-VEGF Refractory Disease: Biomarker Driven Decisions in DME and nAMD

Dr. Rishi Singh:
Alright. So Barry kind of started us off on a conversation around these patients and what we deal with, and I'll talk about anti-VEGF refractatory diseases. This is kind of an evolving definition. I think if you ask 10 retina specialists what anti-VEGF refractatory disease is, you probably have 10 different definitions. So let me try to see if I can come up with some singular definitions that might help us understand. And first of all, when I go through my talk today, I'm going to help you kind of recognize some of these refractatory states. We'll actually reassess some of the biomarkers in that state, and then we'll talk about how we reformulate or talk about what other kind of switching options we might have.

This is a clinical question we get all the time, and I just got it before I walked in the room. It was funny, one of my aunts called me, who I haven't talked to in a long time, and said, "I get injections every 6 weeks," literally, before I walked in the room today, "That's not normal, is it?" Well, sometimes it is normal. That's how we've been having patients come back frequently for injections. She thinks that's a failure. "My patient has had 6 injections; the fluid is still there. What do I do next?" This is a common question we all face in practice.

And so we have some of these refractatory disease state definitions. One we can call a nonresponder maybe, a persistent or worsening fluid after 3-monthly-loading doses with <5-letter visual gain. There's been some really nice sub-analyses in both neovascular AMD and diabetic macular edema, which have shown that this is a negative prognosticator to 12-month visual acuity.

Inadequate responder, a patient who has basically an initial anatomical response, but the inability to extend beyond Q8 or Q6. In those patients, we kind of see those patients necessarily go to another switch therapeutic option because we really want the durability option for our patients. Our patients have difficulty coming in.

And the last is something that we may not be familiar with, but it's certainly within MS literature, about tachyphylaxis, which is that when you have a drug, you're given a drug multiple times, you sort of lose the efficacy over time. And in MS and neurology drugs, that is a common, common situation. In retina, we also think it can happen, and there's been some studies. One of the thoughts is around anti-drug antibodies and how much that might play into that refractatory disease state of nonresponse.

And there's certainly clinical flags you should look for in each of these conditions. I'll talk about some of the reconsidering the diseases, like for example, if it's polypoidal choroidal vasculopathy, you know thinking about when you should look at switching the therapeutic options, and we'll talk about those later in the talk.

These are sort of 4 major signs I look at on the OCT when I look at a patient. So the first is intraretinal fluid and cysts. And if these persist in the first 2 to 3 or 4 months of therapy, these are a really negative prognosticator. And I think there's been a lot of pro and con around fluid and all this kind of discussion, whether subretinal fluid matters or intraretinal fluid matters. Essentially, we've learned that all fluid matters, and I'll show you some examples of that later.

On the right side, you see hyperreflective foci. These are <50 µm in size. These are the white dots you see within the retina. They're thought to be microglial cells and leukocytes that are within the retinal tissues. And essentially, we know that the higher the number of these counts are, the negative prognostication. And there's some drugs that we found that actually have a better response to these hyperreflective foci.

The third is DRIL, the disorganization of the retinal inner layers, and this was pioneered by Dr. Jenny Sun at the Joslin Diabetes Center, which looked at sort of the fact that this inner retina was very sensitive as a biomarker to follow, and if it did not restore its layers or contour, that essentially that was a negative prognosticator to final visual outcome in these patients.

And the last is central subfield thickness variability. And that was initiated with some of the HAWK and HARRIER trials. We've actually done some real-world analyses that show this matters. So patients who have this Yin and Yang effect, or up-and-down effect, of their OCT over time, that can also be a negative prognosticator in those patients.

This was sort of that first category I talked about, which is that all fluid matters. And this is from HAWK and HARRIER, which is brolucizumab at the time versus aflibercept. And what they're showing you here is that you have people that have high disease state activity and low disease activity. And you can see for both intraretinal fluid, for subretinal fluid, for pigment epithelial detachments that this high disease activity essentially has a negative prognosticator compared to the low disease activity in each of these categories. So the answer is whether it's in the PED, the subretinal fluid, the intraretinal fluid, all fluid matters in all of these conditions in neovascular AMD.

And so this is the one we are worried about when we see patients because if they continue to have this up-and-down effect of any of these fluid compartments, that is a bad prognosticator to final vision.

And in fact, when you look at those patients who had high and low kind of central subfield thickness variability, it was actually an 8-letter differential in that patient population. And we did some studies in my prior work that looked at this in the real-world population and found almost a 13-letter difference between the high and low responders. So this is a real biomarker to follow if you see those patients changing over time.

And many times we don't necessarily get a picture of this. I don't know how much you guys use and look at the central subfield thickness on a graph, but that can be very helpful to look at kind of the numbers over time. I think sometimes we don't get to always see that because many of us use PACS [picture archiving and communication systems] systems that don't necessarily ingest the central subfield thickness and are able to see that. But there are some PACS systems that allow you to do that.

The other thing that I'll point out is this hyperreflective foci picture here, which is in YOSEMITE and RHINE. And if you look at those patients at baseline, 99%—essentially the entire population—had some amount of these hyperreflective foci. And again, these monotherapy with anti-VEGF had a poorer prediction response to that. And dual-pathway faricimab treatment had a better response to hyperreflective foci, and that's been shown and published in fact in the past year.

So when do you consider switching? Like, this is a very common question we all are facing in practice these days. And these are sort of the top 5 if you want to call them that. I think the strongest single criterion is really anatomical persistence: when you see that fluid continue and there's no real levy or let go of any of these certain compartments. When they occur after monthly loading doses, and they're still there, that's when we really consider the time to switch.

The failure to extend. We talked about this a little bit more, but Q6 and Q8. If you're in that category, that's a time to extend. The CST variability we talked about before, and this inflammatory signature we talked about as well.

So these are kind of all of those things that will trigger us to potentially switch patients in our practice. And we have newer agents to consider, and there have had some benefit in some of these categories of the switching response. So individually, faricimab has been shown to do better with hyperreflective foci within the central subfield compared to aflibercept 2 mg. It was a 53% greater macular leakage reduction in YOSEMITE and RHINE compared to monotherapy of aflibercept, and you were able to extend patients anywhere from Q4 all the way up to Q16, and that was impressive. So we've had good data on the ability to extend patients with these drugs in this category.

For aflibercept 8 mg, with the higher molar dose, we're seeing greater VEGF suppression. So this VEGF suppression can be almost double what we see with 2-mg aflibercept. And again, when you look at some of the patients that were maintained at Q12 and beyond, 91% of patients with DME were maintained Q12 and beyond. And in fact, many patients were even going to the second year, which is Q24. They are able to go even that far along in their disease state over extension periods of time.

Port delivery is obviously available to us now in the form of the implant. It's been around. Its second-generation implant was released for some modifications that's done. And this again has been another opportunity for us to stabilize central subfield thickness. They've done some really great analyses on these that have shown really well-controlled central subfield thickness variability.

And finally, steroid. I don't know if we talk about this enough, but you'll never hear a person say you're not responsive to a steroid. It's very uncommon to be unresponsive to a steroid. But again, we've learned also that in this hyperreflective foci category, those who receive steroids actually can do well and actually have those hyperreflective foci go away as well compared to monotherapy anti-VEGF.

So we have options available for all of our patients. And let's talk about this patient for a moment. I'll have Ferhina kind of weigh in here. So you see this patient in the office: 62-year-old, type 2 diabetic, 14 years. Hemoglobin A1c is 8.2%. Presenting vision is 20/60. The central subfield thickness is 487. The treatment to date is 4 bevacizumab and 3 aflibercept 2 mg given every Q4. You're looking at this OCT here, what are you thinking about when you see this kind of patient?

Dr. Ferhina Ali:
Of the biomarkers you've mentioned already, definitely persisting disease activity, likely possibly an inflammatory component as well. But the IRF, we're seeing subretinal fluid, hyperreflective foci. So as you mentioned, in terms of the hyperreflective foci, this may be a good patient to consider faricimab treatment for. Getting the dual-pathway inhibition might be helpful, but definitely we're seeing very significant persistent disease activity despite continuous therapy at a 4-week interval.

Dr. Rishi Singh:
Yeah. How about you, Barry? What are you choosing then after the next kind of, and there's no right answer here, right? There's lots of options because what are you picking for your drug options in this patient after this sort of activity? Are you going with 2-mg aflibercept, or are you continuing on with the second-generation anti-VEGF agent?

Dr. Barry Kuppermann:
Well, again, with the DME patient, there is differences that we've seen certainly from DRCR.net Protocol T. Certainly, bevacizumab seemed to be underperforming in the first year. Ranibizumab did catch up. Aflibercept was the star of that study, though there was some catching up. I do like aflibercept 2, but I agree that it's worth trying faricimab. It almost complicates my pathway because I think many of these patients, if they've not had a good response to aflibercept 2, may likely need steroids, so I tend to use a Dex implant for that. But I do try to at least the faricimab to give it a try of at least 3 more injections to see what the response is before deciding.

Dr. Rishi Singh:
Yeah. And I agree with you. If the patient's pseudophakic, I might try a steroid in this patient, but if not, then obviously you have lots of

different options to consider beyond that. So it's a good option to consider.

So just going forward to the next slide, you see that this patient actually had 4 injections of faricimab and over a 4-week period of time, so they actually were able to go 16 weeks with continual faricimab injections, and the visual acuity did improve. The reduction in hyperreflective foci did go down, and the macular leakage was measured and did go down again. So this is where, again, trying to use some of these newer agents can be quite helpful. We were able to extend this patient to Q8 beyond the Q4 visits. Again, we started off monthly. That was a way of initiating therapy when we did that switch in this patient over time.

So just to kind of take this together, we've talked about some of those biomarkers we follow. We've defined the fact that obviously all fluid matters. We talked about some of those issues that we see in our patient populations in regard to nonresponse and how do we re-evaluate the patients and what definitions we apply. I kind of leave that to you, but I've given you some framework as far as what we would see.

Barry, so when you see a patient like that and you're sort of thinking about the next practical step, tell me a little bit about how you get the patient ready. Is it an authorization you send in a month ahead of time to get ready thinking about that? Or is it the day of? Or do you delay that injection and do it the next time? How do you kind of use that workflow in your practice? Because that's very important for us to kind of authorize these patients for drugs and what we're doing.

Dr. Barry Kuppermann:
Well, I tend to talk to them a lot because I like to get them ready for the next step.

Dr. Rishi Singh:
Yeah.

Dr. Barry Kuppermann:
I do get OCTs at every visit and every injection every time. So I'm tracking that, so I'm letting them know how they're doing. If I see that the response has been suboptimal, whatever that means, I begin talking about alternative approaches. And certainly, if I am contemplating a move to a Dex implant, then I spend even more time with that because then there's the side effect profile of cataracts. I engage the patient a lot, and I do try to set them up, and do ask for the authorization as well for the next month.

Dr. Rishi Singh:
We'll ask you, Ferhina. Like, how do you manage that in your practice? It may be a little different than what we do in an academic center.

Dr. Ferhina Ali:
Yeah. So certainly, I think we're all beholden to the insurance companies no matter the setting. But similarly, I'll continue on with the treatment that they've been getting, with the discussion around the plan for a new treatment next time, getting that authorization in the intervening period.

But as Barry was talking about in that first visit, it's really important to set the stage. In the first year, most patients are getting anywhere from 6 to 12 injections. Ideally, in the real world, we know that's really around 3 to 5 perhaps. But letting them know up front, we've got work to do over the course of the coming year, and I think sort of which injection they end up getting, we'll learn as we go.

Chapter 5: Beyond VEGF: Vascular Stability Pathways

Dr. Rishi Singh:
All right, great. So we've really discussed what our current state is, and Ferhina is going to take us through an amazing summary of the future, and so it's really exciting to kind of see some of this stuff come up, and I'm going to turn it over to her. Thank you.

Dr. Ferhina Ali:
Thanks, Rishi. And so we've really learned a lot so far about really excellent treatments that we have, but certainly some challenges operationally, as well as with treatment burden and treatment fatigue with our patients. And so when we're thinking about mitigation strategies, many have been mentioned in terms of operations, but certainly newer treatment pathways can help with our potential

reduction of treatment burden with new treatments.

So when we think about the diseases that we're treating, the common thing being the retinovascular diseases, and there are pillars of vascular stability that we think about when we're thinking of normal vasculature. So what we know is very important, we've leaned on this over the past decades, is the role that VEGF plays in keeping that blood vessel healthy and sort of not superpermeable. And then we also think about a couple of other pathways. More recently, we've talked more about the Ang-1/Tie2 signaling pathway with the recent approval—relatively recent at this point—of faricimab, which is a bispecific antibody, and we'll talk more about that. But this pathway specifically promotes and stabilizes that endothelial-pericyte interaction, so that structural stability. And even more so, we think about the Wnt/β-catenin pathway in terms of really structural integrity of the vasculature within the retina, thereby allowing it to not be permeable and cause leakage and exudation, and all of the things that we've seen on the OCT scan so far. And so we'll look at these a little bit further and talk about potential targets here.

And so that same paradigm we looked at now, if abnormal, we do know increased VEGF certainly plays a role in increasing permeability, blood-retinal barrier breakdown, vascular leakage. Obviously, we've been targeting this pathway now for a number of many years. Ang-2 signaling, this specifically, we can see destabilization of the integrity of those endothelial-pericyte interactions that I mentioned before. And then again, that structural integrity breaks down with the inactivation of the Wnt pathway. So the blood-retinal barrier then becomes compromised, and we see much of what we've seen today in the patient presentations we've already looked at.

So, of course, we are interested in all of these areas. Over the course of years we've had excellent treatments, but there's certainly room for improvement, room for more durability. And when we think about that, we think about potentially new targets as well.

So, as I mentioned, we've seen the combination of VEGF and Ang-2 inhibition with faricimab, bispecific antibody. But also, we think about Tie2 as related to that pathway. One new molecule that's being studied is OLN324. It's a smaller molecule from faricimab, and we'll talk about that in greater detail. But it is bispecific as well in the same way. And then there's EYE201/MK-8748, also a bispecific antibody, inhibits VEGF as well as activating Tie2.

Now the next area that we'll be talking about, which I think is really interesting and exciting, are the tyrosine kinase inhibitors which are further along in sort of their development pathway. We may likely be seeing them soon and using them in our clinic soon. And what we're thinking about here is the potential gains from pan-VEGF inhibition, greater durability that we might see, greater efficacy that we might see in terms of drying and really addressing the leakage process that we've talked about.

So EYP-1901, a bioerodible implant, pan-VEGF inhibition, PDGFR inhibition as well. This one specifically also with a role in JAK1 inhibition to reduce an inflammatory pathway through IL-6. And then OTX-TKI, bioresorbable hydrogel, also pan-VEGF inhibition, and PDGFR inhibition.

And then, lastly, as we looked at briefly and sort of newer in sort of the discussion in our field of treating retinovascular diseases, this Wnt pathway, and it's being studied through EYE103/MK-3000. So this is a tri-specific antibody. We'll look at the specifics of the molecule a little more closely, but this plays a role in sort of maintaining this pathway and maintaining structural integrity of the vasculature.

So you can see here, tetravalent, tri-specific antibody, specific binding sites as you see down below the FZD4 and then the LRP5 up above. And you can see here really that the activation of this pathway is very important for stabilization of the vasculature. Also, this pathway is related to the Norrin pathway in terms of vascular development in the retina. The prior schematic we saw, the implication in some pediatric retina diseases as well in terms of vascular development, but here we're focusing kind of more on the left in terms of self-renewal and repair through mediation of this pathway.

And so we do have already data to share, which is very exciting. So the AMARONE study was a phase 1b/2a 12-week DME study, dose escalation, MK-3000 monotherapy. And you can see here really promising findings in terms of efficacy, both in terms of vision and anatomy. So we see mean vision improvement. So patients received 3 treatments, and you see where they are at 4 months. Improvement of 11-plus letters, very significant improvement in the absolute OCT reduction, as well as percent reduction in that excess CST. So the greater thickness that we see in this disease state of DME, we see significant improvement here, and so we'll look forward to further information for DME.

Here you can see what they did with neovascular AMD. So this is a combination treatment that was studied, MK-3000 as well as aflibercept 2 mg, again dose escalation, small sample size of course, but we see here very positive signal around improvement in vision as we might expect with the combination of aflibercept 2 mg and, also, we've seen so far efficacy in DME in terms of really improving upon the disease state. And so here, absolute anatomic reduction as well as reduction in that excess retinal thickness. And so, we will definitely look forward to the phase 2b/3 trials BRUNELLO and BAROLO for the 2 doses of MK-3000 as compared to active control ranibizumab for DME.

We'll switch gears here in terms of VEGF and Ang-2/Tie2 signaling. We've talked about faricimab already. Rishi has covered this a little bit as well in terms of some of the post hoc findings we've seen through YOSEMITE and RHINE for DME, reduction in macular leakage, as compared to aflibercept 2 mg. Fewer hard exudates, poor tending better vision as we've seen just moments ago, as well as decrease in the hyperreflective foci as well that we saw a little while ago.

In terms of neovascular AMD, we've also seen biomarkers signaling improvement in pigment epithelial detachment with the bispecific inhibition as compared to anti-VEGF monotherapy here with aflibercept 2 mg.

So a lot of work has been done in really understanding the benefits that we get through the bispecific antibody and we are certainly still interested in understanding this pathway more.

Here is a different molecule that's being studied. So, as I mentioned before, this OLN324, also bispecific, VEGF, Ang-2. Here are the anti–Ang-2 benefits that have been studied in terms of restoration of Tie2 signaling, increasing that structural integrity that we've talked about before in terms of the vasculature as well as inflammation in and around the vasculature, in addition to reinforcing those attachments amongst the cells and the vessels within the blood-retinal barrier.

Anti–VEGF-A benefits we've known now for many, many years, as you can see listed down to the far left. And so here, the interesting things of really kind of to know about this molecule in terms of compared to what we currently have, so potential higher potency in terms of the Ang-2 inhibition, 60 times greater as has been studied in the lab. Compared to faricimab, it is a smaller molecule, so 41 kDa, 1/4 of the size, potential for better tissue penetration. And then here, you can see in terms of the VEGF component, a higher molar dose as compared to faricimab, aflibercept 2 mg, and aflibercept 8 mg. So we really look forward to the potential of the smaller molecule potentially more potent and see kind of how these patients do.

Here are some early results here from the JADE study. You can see here improvement in vision, faster and greater retinal drying here, and of course they, interestingly enough, compared to faricimab, as is appropriate, same MOA but different molecule, to really kind of understand the potential value-add here from this molecule. So we see the improvement in vision and improvement in anatomy. That was in DME, and here in neovascular AMD we're seeing that as well, so we will look forward to later phase studies there for this specific molecule.

Now switching gears a little bit to EYE201/MK-8748. So, as I mentioned, this is the VEGF Ang-2/Tie2 kind of combination potential here, and this was presented earlier today, as Dr. Kuppermann mentioned, but being studied for the 1/2a RIOJA trial for macular edema in the setting of branch retinal vein occlusion, which of course we know is very vascular driven. And so this is a tetravalent antibody. You can see the schematic here, and we'll be interested in seeing these results as well.

And I think they were presented just earlier today, but this was dose escalation also, and you can see here 3 monthly injections were given. Improvements in vision were observed, and the safety profile here was reassuring. Mean improvement in vision also significant, and so we'll look forward to the phase 3 programs here as well.

So TKIs, as I mentioned, tyrosine kinase inhibitors. This is pan-VEGF inhibition. You can see here in the schematic down below, acts intracellularly and also very broadly as compared to the monotherapy and bispecific therapy you can see up above, with really the potential for significant efficacy in terms of that vasculature being sort of stabilized in these disease processes, and then also the potential of durability based on the delivery platform that I've spoken about.

So EYP-1901, vorolanib, as I mentioned, also has this additional MOA of JAK1 inhibition and playing a role as an inflammatory mediator, as well as has been studied in vitro. And you can see here the results from the DAVIO 2. So this is the neovascular AMD phase 2 trial. You can see the primary endpoint was met in terms of vision noninferior as compared to aflibercept 2 mg here on label, and you can

also see a reduction in treatment burden. So all of these things that we spoke about earlier in the hour about the significance of the treatment burden, patients being lost to follow-up, care coordination being attempted from a variety of different avenues, but still these are significantly challenging areas that treatments that may potentially last longer while maintaining good efficacy, good vision, will certainly really serve our patients' needs quite significantly. So we're excited about the reduction in treatment burden here.

And you can see here the results for VERONA. This was for the treatment of diabetic macular edema. Again, here the primary endpoint was met with improvement in vision, and you can see that in terms of the treatment burden reduction in that as well, in terms of significant improvement in terms of supplement-free rates as compared to the control arm.

Now, I mentioned OTX-TKI, the SOL-1 results here so far. We've seen mean change in BCVA and CST in neovascular AMD, as you can see here, really impressive. Again, also showing reduction in treatment burden, which we are really quite interested in. So maintaining vision and anatomy, with most patients being rescue-free, sort of based on how these trials are designed. We will look forward to the noninferiority trial results as well for those and the phase 3 program for EYP-1901.

So, as has been mentioned, corticosteroids still a really important mainstay in our practice. We definitely have anti-inflammatory effects, the safety profile being a little bit different, but as was mentioned in one of the patient cases we looked at just earlier, one of those being really a good candidate for improvement in that very significant disease activity we were seeing in the form of intraretinal fluid, subretinal fluid, hyperreflective foci, that corticosteroids really do target multiple inflammatory pathways for providing a really robust effect in terms of improving the anatomy in combination with anti-VEGF, or even on its own. But of course, many of us are starting with anti-VEGF as a more first-line, safer treatment. But it's important to keep in mind that we do have corticosteroids in our toolbox, and you can see here the difference in terms of its targeting as compared to anti-VEGF therapy, bevacizumab, in terms of that anti-inflammatory pathway.

So overall, we really do have a lot of currently available treatments that are quite effective at improving the disease states for our patients, maintaining really good vision. We do need sort of more time, more durability. We're excited about new pathways of targeting retinovascular stability for our patients, and we'll look forward to some of these newer mechanisms of action playing out in their later clinical trials, and hopefully we will have these available for our patients in addition to what we have today.

Chapter 6: Key Takeaways

Dr. Rishi Singh:
One of the significant patient populations we don't have a treatment for is those who have ischemia. We're seeing a lot of those patients necessarily that over time, and we know that if we've done prospective studies on anti-VEGF and shown that the outcome ischemia doesn't really matter in the patient populations. Still, none of those treatments have applied that right now.

I think the other piece that you talked about here in general is like when you look at our anti–VEGF-treated population in general, most of them are in Q8, Q9 weeks of therapy. I mean, I think very few of us get out to Q12 and beyond. The tyrosine kinases seem very, very impressive right now from that standpoint. So that'd be interesting to kind of see how that plays out next. We're supposed to receive the noninferiority data for one of the studies in the fall and another study in the fall as well. So it'll be good to see that.

But we've kind of summarized a lot of different datasets here, new data we're seeing from the new studies, all of you see the biomarker data we discussed before and how that can impact therapy, when we proactively might switch patients, and when vascular stability matters, and some of these new emerging therapies.

So I'll turn it over to Barry for this first question. During a treat-and-extend protocol, if a patient presents with new fluid after the extension, what do you do then? So let's say you're on Q10 weeks of a treat-and-extend paradigm, the patient presents with new intraretinal fluid that wasn't there in the prior stuff, what would you do? Would you go back to the last interval, or would you continue on this interval if the vision is stable? How do you kind of figure out what to do with treat-and-extend?

Dr. Barry Kuppermann:
So again, I'm going to answer on the current therapeutic approaches using the intermittent biologics. When we've got a drug delivery system on board, whether it's a TKI or a port delivery system or the future gene therapy, our thoughts about fluid will be different if we know that there's actually drug on board. But we know in treat-and-extend, by definition, that the drug is long gone after somewhere in that 4- to 6-week range. And so anything beyond that, the patient is having a drug holiday.

So I do tend to treat at that time, and arbitrarily, I tend to do 2-week increments. It depends on how much fluid. If there's just a tiny bit of fluid, I'll just mention that a tiny bit of fluid, I might just keep it at that same interval. It lets me know that they still need therapy. If it's a modest amount of fluid, I ratchet back by a week. If it's a fair amount of fluid, I'll cut back by 2 weeks.

Dr. Rishi Singh:
Ferhina, when you talk about treat-and-extend, I think people are kind of honing in on is it a week extension, 2-week extension, 4-week extension. Do we have any data that you can cite, or what is kind of your overall approach in your clinic?

Dr. Ferhina Ali:
Sure. So great question, and I think definitely the mainstay in our practice. I think for me over the many years, I've definitely leaned into an extension or a reduction in treatment interval of 2 weeks. Now, here and there, there may be a specific reason for a patient to have a 1-week change, but overall, I anchor around 2 weeks.

But as we know, with the approval of both faricimab and aflibercept 8 mg, those trials allowed for extension at 4 weeks at a time. Of course, that's tied to their retreatment criteria and a variety of other factors, but we do know that patients did well, maintained good vision. As long as you're continuing to see them, likely that is a reasonable strategy as well. And I think many retina specialists have employed that more since these trials. But I wouldn't say it has necessarily become the norm. I do stick to 2 weeks.

And then sometimes you know for what was mentioned before, for a patient that's showing recurrence of disease activity, certainly you can shorten the interval and see how they do. But if there is a second-generation treatment that they have not yet been on, there is the possibility that they might get more time with another drug, even though we know that the initial treatment did do a good job of controlling the disease.

Dr. Rishi Singh:
So go ahead, Barry. You were going to say something.

Dr. Barry Kuppermann:
No, I was just going to say I was kind of curious, Rishi. I agree with everything you said, Ferhina. And again, I tend to use 2 weeks. We know from the clinical trials there was 4 weeks, but that was a very different retreatment criteria, as you highlighted.

How about you, Rishi? Have you expanded out to 4-week intervals?

Dr. Rishi Singh:
Yeah, so. No. So actually, I do do 4-week intervals. I think that there has been data. Obviously, we've seen that in, was it the ARIES study or the ALTAIR study? Which 1 of the 2? One of the, well, yeah. So that did have that extension period. I think you could learn a lot from that study and what it was. There wasn't a detrimental effect on visual acuity in the rapid extension period. So I do do 4-week extensions typically in my practice in general.

What about this Wnt pathway? Obviously, this is new to us. We've learned a little bit about Tie2 activation. But Ferhina, what advantages do you think Wnt pathway disruption might be of value to restore that?

Dr. Ferhina Ali:
Yeah. So sure. So we do know from sort of translational work that it plays a role in retinovascular stability and that blood-retinal barrier in terms of our diseases. A big cornerstone of them is leakage through the vasculature and disruption of the normal structural integrity of the retina and the neighboring sort of that blood-retinal barrier. So I think there's good science behind it.

We've now seen results that I've mentioned with the AMARONE trial, both in diabetic macular edema and neovascular AMD, showing either for sure with monotherapy, we're seeing very good improvement in vision, anatomy with multiple doses. All doses were found to be effective. And then in combination, we also see improvement there as well. I'll be curious, for sure, to see what we might learn in terms of durability. But so far, there's a signal in terms of efficacy, definitely with this pathway.

Dr. Rishi Singh:

Yeah. When we think about some of these newer agents, Barry, like in the near-term future, we're going to have potentially some of these products. Like the closest to us is probably the tyrosine kinase inhibitors. How do you feel like you're going to incorporate those into your practice? Is this going to be an and/or, or is it going to be exclusively 1 of them or 1 tyrosine kinase and not the anti-VEGF? How do you kind of think about that in your practice, given the data?

Dr. Barry Kuppermann:
So again, the tyrosine kinase inhibitors are pan-VEGF blockers. They do a few other things too. They're weaker than our biologics. They're small molecules, so that's why they can be packaged into a drug delivery system. So I'm excited about that. I'm a big fan of drug delivery. Love to extend the intervals. Again, as we try to do our treat and extend, even with the second-generation drugs, you know there's not a lot of our patients that get out beyond 12 weeks, and very few that I have out to 24 weeks. That's kind of my new upper limit. Since we learned that from the trials, we can keep going further. But certainly less than 10% have achieved that.

I'm very excited about the possibility of with the TKI in that drug delivery system getting a greater percentage of our patients out to 6 months. I think that'd be a huge win if we can achieve that. Again, the data we'll have to see, and then have to test not just the data, look at the data from a clinical trial, but test it in our hands in the real world because we've frequently seen that we have a different interpretation.

So, still, it looks like in those studies, I'm probably going to start with the biologic. And so I'd start with whatever the de jure is, like, one of the aflibercepts or faricimab, and then see. If I can treat and extend if it's one of those rare every-24-weekers, maybe I just stay there. If I can only extend out to 8, 10, 12 weeks, then certainly when I've reached that limit of extension, as we get more and more comfortable with those TKI drug delivery systems, I'd be more inclined to then switch over to a TKI in the drug delivery system and then look carefully for the recrudescence and monitor them, probably—I don't know what interval—probably every 3 months or something like that. But we're going to have to learn a lot if and when it gets approved.

Dr. Rishi Singh:
Yeah. How about you, Ferhina? What would you do? How are you going to manage like these tyrosine kinases?

Dr. Ferhina Ali:
Sure. So I think it will be very exciting to have I think the potential for a 6-month drug. But we'll also be thinking about sort of the trial design, how they were approved, the combination of anti-VEGF that is needed up front, and then we'll be thinking also about what the payers may allow in terms of the treatment pathway for these patients. But I think in the initial period we're likely going to be seeing our patients nearly as frequently, quite initially, but certainly I think we will get more time, and I'm very excited about that.

And then I think from a long-term standpoint, likely it's going to be some combination of bolus treatment with sustained sort of on board. And I agree with Barry; I think the excitement around the small molecule, the delivery platform, all of that is very exciting and potentially paradigm shifting. But we'll learn a lot in the beginning as we go, and the payers will certainly guide us as we do that, I think.

Dr. Rishi Singh:
Great. Well, I want to thank both of you for coming and presenting. Thank you all for the audience for participating