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Redefining Durability in nAMD: The Science and Strategy of Sustained-Delivery TKIs

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Chapter 1

Dr. Ash Abbey:
Hello, I'm Dr. Ash Abbey. With me today is my friend and colleague, Dr. Rishi Singh. Today we'll discuss the clinical rationale for sustained-delivery tyrosine kinase inhibitor therapy for the treatment of neovascular AMD.

Before we begin, I'll briefly summarize the issue of durability in the treatment of neovascular AMD. For the first 2 decades of anti-VEGF therapy, durability was often discussed very simply: How many weeks can we go between injections without losing control? That remains important because injection burden affects patients, caregivers, physicians, staff, and ultimately adherence.

But I think the concept of durability has evolved. Today we are not only asking how long can I extend the interval, we're also asking how consistently is the pathway suppressed, how stable is the anatomy, how often does fluid recur, and how many rescue treatments are needed, and also does the patient maintain vision over time?

That is why sustained-delivery TKIs are generating so much discussion, they introduce a different pharmacologic concept, not simply binding VEGF outside the cell, but potentially suppressing VEGF-receptor signaling inside the cell over a prolonged period of time.

There are really 2 challenges for clinicians. First, we have to translate mechanism into clinical meaning. A broader or more continuous mechanism is interesting, but we need to know whether it translates into vision, anatomy, safety, and treatment-burden outcomes.

Second, we have to interpret divergent phase 3 trial designs carefully. EYP-1901 and OTX-TKI are both sustained-delivery TKI approaches, but their pivotal trials are asking different questions.

So, Rishi, when we talk about durability today, are we still just talking about injection interval?

Dr. Rishi Singh:
Yeah, Ash, that's a great place to start. You hit it on the head. Durability, up until now, was really a scheduling term, and we could get patients out 2, 3, 4 additional weeks, but we were tolerating fluid, we were tolerating vision loss sometimes, really for the burden of

treatment. But, as you said, mechanistically, we're really looking at durability now as the way to suppress the pathway.

And this is where kind of these newer agents fit into our practice. When you look at the current VEGFs that are available—anti-VEGFs are available—aflibercept, ranibizumab, bevacizumab, faricimab, they all work on the extracellular pathway. They are obviously good at sequestering the VEGF ligand, and then that does help consume and could clear those signals. But after it's removed from the system, the signal returns, and so suppression is over, and it continues on.

Tyrosine kinases are fundamentally very, very different. They're small molecules, they've been around for many years, they've been in other domains of medicine that are available, and they block the phosphorylation cascade downstream from the VEGF receptor, so it's not just what the VEGF receptor shows up at the door, it's the receptor can't signal and the pathways and quiet, so ultimately leading to that suppressed pathway.

And I think 2 things follow. First, we know that these are pan-VEGF inhibitors, when you look at both vorolanib and axitinib, both of them affect VEGF receptor 1, 2, and 3, as well as PDGF receptor and FGF receptor, so it's a pan-VEGF inhibition rather than 1 or 2 ligands.

And second, vorolanib also has been shown at physiological levels to inhibit the JAK1 pathway, which blocks IL-6 signaling. We know that this is an important pathway, Ash. You've seen it recently in data from both uveitic macular edema and diabetic macular edema, and of a benchmark study that was released completed. And we know that the biology does work if it's properly given, and we're seeing the same sort of pathway emerge for some of these tyrosine kinase inhibitors.

Dr. Ash Abbey:
Yeah, I think that's a great point. I mean, we often talk about the current ages that we're looking at, as just a let's go 8 weeks, let's go 12 weeks, let's go 16 weeks, and it's in this case with the sustained-delivery TKIs, I feel like we're getting that intracellular receptor pathway suppression is not just going to hopefully delay recurrence, but it's going to also reduce the amplitude of recurrence, so we're not going to get that sawtooth pattern, hopefully as much, where we see where we're doing the bolus injections and getting this kind of up-and-down effect on our anatomy and possibly on our vision as well.

And I think we've seen for previous studies now that when we do have more of a consistent dosing, where we don't have a sawtooth pattern and fluctuations in anatomy, we often get a better long-term visual outcome as well, so hopefully that will pan out with the phase 3 data for both these trials as well.

How do you explain the mechanistic difference to a colleague or to a patient in practical terms for these 2 TKIs?

Dr. Rishi Singh:
Yeah, it's sort of that faucet analogy we've used before in some of the prior work we've done; anti-VEGF therapy is like catching every drop of water that comes out of that tap. You obviously can be very good at it, but it requires a lot of skill. But the moment you stop catching it, the water is still running, and so you have to keep coming back, and maybe your bucket gets full.

A tyrosine kinase inhibitor is actually turning off the valve behind the wall that turns off the faucet altogether. And I think patients understand that. They get the fact that obviously this is a durable approach that might turn the signal off for a period of time, and paired with anti-VEGFs, which as many of these are paired with anti-VEGFs, can be a 1-2 combination punch to really talk about how we can both suppress the pathway, as well as cut off the intracellular signal, as well as mop up all the extracellular VEGF, so they work in concert with each other and partnership to really to act on 2 different aspects of this pathway.

Dr. Ash Abbey:
Yeah, that's a great point. I really think it's important for both clinicians and patients to understand that both of these therapies are probably not going to be just use this and that's it. We'll probably use it in combination with our current best anti-VEGFs, if possible, like our second-generation anti-VEGFs to get the best possible outcomes for our patients.

And I think we want to make sure that people know that these treatments do behave differently than our regular anti-VEGFs, and with kind of more sustained delivery, the hope is that the eye has more continuous pathway suppression rather than a repeating cycle of kind of strong treatment followed by gradual wearing off as well.

So thank you. In Chapter 2, we will be discussing sustained delivery platforms and the biology of continuous exposure.

Chapter 2

Dr. Abbey:
Okay, welcome back. In the first chapter, we talked about concepts defining durability in the management of neovascular AMD. In Chapter 2, we'll discuss sustained delivery platforms and the biology of continuous exposure.

Rishi, can you tell us about these platforms that are currently under investigation?

Dr. Rishi Singh:
Yeah, so the key I think understanding that I think clinicians have to realize is that a tyrosine kinase inhibitor is a small molecule, and if by itself it won't alone give you durability. These are clear from the vitreous very quickly, because of their size and because of their half-life. So a delivery system is a therapeutic strategy to really keep it around for a longer period of time; it's not really a packaging decision as much as it is a platform decision, because it would be ineffective if it was just injected once in that platform.

So the first is EYP-1901. We're well aware of this technology from prior drugs we've had in the space. The kinetics have shown in animal models and in human studies to go about 9 months, and it can be stored at room temperature, which is a really great advantage for clinicians like myself and you. We have a fridge that's always overflowing with drugs these days, and so being able to keep this drug potentially at room temperature is a nice opportunity.

The second is the OTX-TKI platform. Axitinib is a bioerodible hydrogel. This also has been around for another indication, and roughly present for about 8 to 9 months by some of the studies that were done.

And I think that there's a big distinction between these 2 pathways. Again, the extended-dosing interval and maintaining continuous receptor inhibition are not the same thing. Obviously, we know that when you put these inserts in the eye, that it's suppressing the pathway for a period of time. That, in essence, is where the drug is being affected.

The actual delivery platform may or may not persist after that period of time. We've seen this recently from one of the OTX-TKI platforms, that the actual hydrogel does dissipate and does become present in various tissues of the eye. Again, I think that's an important distinction to understand, kind of if that has any effect on the patient, but it is something that we see in some of these platforms that the delivery system may persist while the drug doesn't get eluted, so we might need to re-inject this platform at various periods of times in between those intervals.

Dr. Ash Abbey:
Yeah, that's a great way of discussing the different platforms here. I think a lot of times retina specialists are comfortable judging the drugs by the injection interval, but we may underappreciate how much innovation is actually happening in the delivery technology itself, and also what potential maybe adverse events could happen as a result of having these other delivery platforms that we're maybe not as familiar with now.

So the platform really does determine, though, whether the drug exposure is high enough, long enough, predictable enough, and repeatable enough to matter clinically, but it also affects the office workflow, kind of the patient experience, safety monitoring, and eventually how we think about re-treatment, like you said.

So it's almost like we got to be thinking on these agents as not just what is the molecule, but we got to ask: How is it delivered? How consistently is it released? Can it be repeated? And how often can it be repeated? And what happens if disease activity breaks through during that time as well?

So, Rishi, what does continuous inhibition potentially change in the long-term fluid control?

Dr. Rishi Singh:
Yeah, so this has been an insight I think, Ash, you and I have had over many different studies in the past few years. We've seen this kind of effect of this sawtooth pattern. There's a terminology called central subfield thickness fluctuation, which has been around for a little bit. We've seen it initially in some of the CATT trials, as well as some more recent studies, where we have found that when patients

have increases and decreases in retinal thickness, that does lead to a negative prognosticator as far as final visual outcome.

In fact, we did a real-world study that showed that if you had the highest level of this central subfield thickness fluctuation in your population of patients, you could have almost a 12-letter differential between those patients who had little central subfield thickness fluctuation. So, it's a huge impact as far as visual acuity and potentially long-term outcomes in regard to disease activity and atrophy, and sort of the fibrosis effect we see in patients. So, can you control patients better? That's the important, I think, question on the table.

And DAVIO 2, this was a non-inferiority trial design with aflibercept, vorolanib was given and it met its outcome. And 80% to 85% to 90% of patients had a reduction in supplemental and burden, with roughly 2/3 of patients really going rescue-free out to 6 months. So they obviously had the right anatomical and visual response to meet that criteria. They didn't have the same fluctuation that we saw in our normal patient populations that we see with 8-week aflibercept.

On the axitinib side, we saw a very similar program in their phase 1, where they showed an 89% reduction in treatment burden in 1 year with a median time to supplementation around 44 weeks. So again showing good durability both in visual and anatomy outcomes comparable to 8-week aflibercept.

So this is the big, I think, opportunity is really reducing the central subfield thickness variability, which we know has an impact on the final visual acuity outcome. And I think that this is again where clinicians will obviously have the opportunity to maybe control their patients better, not have those 3- or 4-letter visual declines that we're always so concerned about, that's the one that we always I think, Ash, you and I can agree, we never want to see that in our patient population. So this gives us an airbag effect, or at least a better control effect. It's a huge win for our patients, ultimately.

Dr. Ash Abbey:
Yeah, I totally agree. The way I think about this in clinic is that we're currently using anti-VEGF regimens as more of a reactive treatment, even when we use treat-and-extend, we're constantly looking for that long and safe interval before disease activity returns.

Whereas with the sustained-delivery platform, we're almost moving towards a more stable suppression model, so that doesn't mean that we stop monitoring our patients, it doesn't mean that rescue therapy disappears as well, but it may change the mindset from kind of this more episodic suppression to continuous control, which hopefully will give us those better long-term visual outcomes.

So, thanks. In Chapter 3, we'll be discussing the clinical trial design for EYP-1901 and OTX-TKI. Stay tuned.

Chapter 3

Dr. Abbey:
Okay, welcome back. In Chapter 2, we discussed investigational sustained-delivery platforms for TKI therapy, and now in Chapter 3, we'll look at the clinical trial designs for these treatment approaches.

Rishi, can you give an overview of these trials and the relevance of the differences?

Dr. Rishi Singh:
Yeah, so if you've listened to the last 2 chapters, this is probably the more important one for the retina specialist, because these 2 programs are really asking very different questions against different endpoints and different comparators. Let me lay them side by side for you all, so you can understand them better.

EYP-1901 is looking at in the LUGANO and LUCIA trial a large non-inferiority trial design for 2 large global studies. There are approximately about 400 patients each in the study, comparing EYP-1901 to every 6 months against on-label aflibercept every 8 weeks.

That primary endpoint is the mean change in best-corrected visual acuity from day one, averaged over 52 to 56 weeks, with a framework of non-inferiority. And, Ash, you're aware of many non-inferiority trial designs the past few years were something that retina specialists understand very well, the faricimab studies were non-inferiority trial design, so we understand kind of where they fit into our population and how we can interpret them.

The topline data from LUGANO is expected around mid-2026, with LUCIA following later this year. So this is a continuous delivery system given over every 6-month period. So we're going to have really good data on repeat dosing as well, which I think is very, very important to understand how that might compare to the standard-of-care medications that we have in our practices today.

OTX-TKI had the SOL-1 study, which was recently released the data, we all saw, the superiority trial design. This is a different architecture altogether. The superiority trial design was done under a special protocol assessment by the FDA, where they did a single dose of OTX-TKI compared to a single-dose aflibercept after a loading phase in 344 treatment-naive patients. And the primary endpoint here was a responder endpoint. It was the proportion of patients who maintained vision who did not have 3 lines of vision loss over the reported portion of time. And it hit its superiority outcome. OTX-TKI had 74% of patients maintaining vision versus 55% of patients on aflibercept, with almost a 17.5% risk difference between these 2 populations, for a very strong P value.

The week 52 durability assessment found again those rescue-free rates favored OTX-TKI versus aflibercept. And this is sort of really helpful because this study really helps us understand that there is a signal in regard to durable tyrosine kinases in the eye. And again, that's really helpful to understand for the lay retina specialist that this pathway does work, it does actually have a benefit, and so it really is, I think, reassuring to understand that.

So I think that once you understand these 2 studies and you understand the differences, I think it's important to understand that these trial designs are very, very different.

I just talked to you about the SOL-1 study, which is the percentage of patients maintaining a threshold of vision after receiving a significant letter improvement. They were only eligible to be in the SOL-1 study if they saw that letter improvement, so they had to have at least a significant improvement from baseline in order to be enrolled.

That might have some applicability in regard to what we would see in our clinical practice. Ash, not every patient you inject in practice has a 5-letter or a 10-letter improvement from baseline, and so I would ask the question of, like, how many of your patients will actually fit this population, and maybe that's something that we'll understand better when the drug comes out.

The other part to this, I think, is the non-inferiority trial design benefits in many cases. We know that these are combination treatments, as we talked about in Chapter 1 or 2, that really, we're going to expect to give anti-VEGF in combination with these tyrosine kinase inhibitors, this 1-2 punch kind of thing. And just having a trial that looks at 1 drug given over time and not necessarily redosed over time doesn't really help us as much as a non-inferiority trial design, because both the drugs are being given on intermittent bases for rescue, but also for repeat bases for every 6-month injections.

So, again, the take-home, I think, from all of this is that these are 2 programs that are all both very encouraging, both to reduce treatment burden, but cross-trial comparisons are going to be very imperfect. If anything, like I can tell you, we've tried with cross-trial comparisons. I think you saw that from the aflibercept 8 mg to faricimab. Everyone's trying to make cross-trial comparisons because at least the control arms are the same, but realistically you can't do that, and certainly not in these trials can you do cross-trial comparisons.

Dr. Ash Abbey:
Yeah, I think that's such an important point. I mean, these trials were extremely, extremely different in the way they were designed, and so it's nice in the way that we see that sustained-release TKI works up-front, and to a certain degree, and we can also see it as a maintenance agent and a non-inferior agent to our current standard of care with the EYP-1901 trial as well. So we've got both kind of at least datapoints, which is helpful, but they are 2 different products as well, so the cross-trial comparison just doesn't really work very well in these situations.

I think we should be disciplined about this stuff, so we should always be asking, what was the comparator in these trials? Was the endpoint mean change or responder threshold? Was it trial superiority or non-inferiority? And how did they handle rescue injections in the trials themselves? Those specifics actually matter in how we interpret this data. And also, what happened at the anatomy over the course of the trial for these patients? Was it fluctuating a lot, and they still tolerated it based upon the retreatment criteria? Was the vision going up and down as well? I think these are all questions to be asked in order to really understand better what we're getting with these products.

And then real-world data will help as well. If we get these in our hands, actually we can hopefully have some nice real-world trials to show how we can be able to best use these in combination, as you said, with our anti-VEGF therapy to get the best possible outcomes for our patients.

This has been great. So, in Chapter 4, we're going to explore practical integration of sustained-delivery TKI therapy into clinic and summarize the key points of our discussion.

Chapter 4

Dr. Abbey:
Welcome back. In this chapter, we'll talk about how to integrate sustained-delivery TKI therapies into practice, and the key learnings from today's discussion.

Rishi, what practical tips do you have for our audience regarding integration of these therapies into the clinic?

Dr. Rishi Singh:
Yeah, they're probably 3 particular things I would want to communicate to anyone clinically about these drugs.

The first is overrating these durability signals. It's exciting to see an 85% to 90% burden or reduction. But these are still in their investigational trials. Hopefully, they all read out appropriately, and we all can celebrate the fact that they're going to have good both safety data and clinical data that is replicated within the phase 3 that's helpful.

The second is, I think, when you communicate this with patients or providers, or wherever you're speaking about, you always want to communicate the uncertainty of the outcome. You're going to get months of potential durability, is a reasonable hope, but this idea of like a one and done scenario is not a phrase I would use for any of these drugs. Right now, at least, I think that there is some thought around maybe some super responders, maybe we'll see more of that information and understand that better, and how that could be.

The third is I think again rebuilding the counseling conversation around mechanism. We talked about the fact that these are slow-release implants, that they turn off the faucet or signal for the situation, but supplemental treatment will be necessary. These are not in isolation. It does reduce the burden but doesn't abolish the follow-up that's needed for these patients. And so, maybe with the advent of home OCT or different kind of mechanisms in the office, we'll learn about how we can potentially see these patients and see them on a regular basis. And again, this is, I think, up for discussion. Ash, do you see these patients every 2 months, every 3 months, every 4 months? I don't really know yet. I think we're going to learn from the data, like how to guide our follow-up periods, which I think is probably the most open-ended question right now for any of us doing this sort of work.

Ash, I'll turn it over to you. If approved, what would you need to be true for you to integrate this in your practice?

Dr. Ash Abbey:
Well, I think several things would need to be true for me to integrate a TKI into my practice.

First, I would need to see convincing visual acuity preservation. I mean, reducing treatment burden is certainly valuable, but not at the expense of vision. And so, in wet AMD still, we have to make sure that we prioritize maintaining as much vision as possible, as you were noting earlier too.

Second, I would really want to see reliable anatomic control, so if the therapy does reduce injections but allows recurrent or persistent exudation in a meaningful subset of patients, then we need to know exactly who those patients are and how to manage them as well.

Third is obviously safety has to be very clear with these treatments. I want to understand inflammation, some symptomatic floaters, IOP, retinal vasculitis events, occlusive events, endophthalmitis risk, and what happens with repeat dosing. Are we compounding the potential adverse events as we continue to treat them repeatedly over time?

And then fourth, I would need some practical re-treatment guidance, I think, which is eventually going to have to come from our own real-world experience. But if fluid recurs, do I rescue with aflibercept? Do I redose with a TKI if it's been 6 months or more, or is there an

on-label indications that I could use it earlier? Do I combine? How soon can I redose? These are all questions that we're going to have to answer, and once we have it in our hands. And also, should I tolerate intraretinal fluid, subretinal fluid? There's even a little bit of toleration of subretinal hemorrhages, smaller ones, in these trials. So is that actually okay? Are we actually doing harm to the patient by leaving those alone if we have a TKI on board? I think these are unanswered questions still, but I think those are things to think about once we have it in our hands in the real world.

Finally, I want to know where it fits. I might think differently about a stable patient who has already demonstrated very good anti-VEGF responsiveness but requires frequent injections, versus a newly diagnosed patient with aggressive disease, versus, say, a monocular patient or a patient who has difficulty returning for visits. These are all considerations where maybe we'll be leaning more towards a TKI over regular anti-VEGF therapy, or maybe we're leaning more towards anti-VEGF therapy alone for different types of patients and their different kind of disease response as well.

So yeah, I think it's a complicated question, but I think all those factors need to be considered before getting these out into the patients that we're going to be treating in the clinic.

So before we close, can you tell us one misconception about TKIs you'd correct immediately?

Dr. Rishi Singh:
Yeah, I think we've kind of talked about it, but I think that it's just not a long-lasting anti-VEGF. It's a totally different mechanism of action. It's a pan-VEGF receptor inhibitor, and the durability comes really from the delivery platform and not a bigger dose of the same idea. I think we've all seen that recently in clinical practice. And while higher doses are probably valuable, this is not the same thing. It's a different drug altogether.

Ash, what would you say?

Dr. Ash Abbey:
I kind of would think about the correcting the idea that durability means almost no monitoring. I think we really do need to watch these patients closely, even if we think that these agents have an effect for 6 months, 9 months. We're going to be wanting to see them in the clinic, still do an OCT, still examine them well, and just make sure that we have a plan for rescue treatment if disease activity returns.

Rishi, what about one mistake clinicians make about interpreting the trial designs?

Dr. Rishi Singh:
Yeah, I think, again, comparing across these trials is not easy, and that's a headline number, but it doesn't mean you can really equate them. When you see a result like a 74% responder rate against a single dose of aflibercept and then a mean letter non-inferiority difference against 8-week aflibercept, they're answering 2 very, very different questions.

So I think the clinician needs to understand that you need to match the endpoints in order to understand the difference between the comparators, but we don't have that right now, and so that's a big, big opportunity for us to understand.

Dr. Ash Abbey:
Yeah, I mean, I think durability claims across trials without asking whether the comparator, endpoint, rescue criteria, and patient population were the same, usually that's a mistake, and they are very much not so in between these 2 different trials. A week 36 responder endpoint is not the same as mean best corrected visual acuity change at 1 year. And a superiority trial against a single comparator injection is not the same as a non-inferiority trial going against on-label aflibercept, and I think those distinctions really do matter in how we interpret the trials and how we compare them as well.

So, one last question. What is one question every retina specialist should ask when reviewing durability claims?

Dr. Rishi Singh:
Well, I think the first is, how are those durability claims being made in regard to what is the measurement or the rubric of what they're following in the clinical trials? Is it 75 µm of retinal thickness change, visual acuity change, hemorrhage? What is the endpoint there?

I think also we just should maybe look in the mirror sometimes and look at what we're doing in clinic. Are we really getting the durability that we're hoping to achieve with these drugs by extending the intervals out? Are we tolerating fluid in our patients where we really don't have the durability we hope to have, but we're just artificially increasing the interval of dose?

I think that those are comparator claims that we're going to have to answer in the near-term future, and hopefully these studies will help us kind of define that.

Dr. Ash Abbey:
Yeah. I mean, I think it's important to think about, is this durable compared with what exactly? Is it no treatment? Is it just a single injection? Is it 8-week aflibercept? I mean, what are we comparing to, at least in the trials? And how can we extrapolate that out into our own clinical practice? I really would be thinking about, like you said, how much fluid can we tolerate in a durable claim, saying something is durable. How much intraretinal fluid versus subretinal fluid? And is it okay to tolerate intraretinal fluid, which we know may cause more long-term damage to the vision, potentially in patients at least who are getting bolus dosing with anti-VEGF, so does that change? Does the calculus change when we have this sustained-release delivery device on board?

So it's definitely complicated, but if a therapy reduces treatment burden while preserving vision and maintaining anatomy and minimizing the rescue therapy, and also demonstrating a favorable safety profile, then it could be very meaningful for our patients and our practices, but we need to interpret all the data carefully and kind of integrate these therapies responsibly if they're approved.

Well, Rishi, that's all the time we have today. So, I want to thank our audience for listening, and thank you for joining me and for sharing your valuable insights. It was really great speaking with you today.

Dr. Rishi Singh:
Yeah, it's a real pleasure, Ash. Thanks for having me, and thanks to everyone for listening. Always great talking

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