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Meeting Eye-to-Eye: A Patient-Provider Exchange on Improving Treatment in nAMD Through Sustained Delivery

Dr. Khanani:
Hello, and welcome to this CME webinar meeting, *Eye to Eye: A Patient-Provider Exchange on Improving Treatment for Neovascular Age-related Macular Degeneration through Sustained Delivery*. I am Arshad Khanani with Sierra Eye Associates in Reno. Here are my disclosures. And I'm honored to co-chair this program with my good friend Dr. Dante Pieramici from California Retina Consultants. And we are very excited also to have Doreen, one of my longstanding patients here, and we'll have a discussion with her about her disease and how living with neovascular AMD has affected her as well as the treatment burden and other issues.

You know, we have been in practice for decades, and really, for patients with neovascular AMD, we really didn't have any treatments in '80s and '90s. Thermo laser was introduced followed by submacular surgery, and really, none of those techniques were improving or stabilizing patients. PDT was introduced in early 2000s and really slowed the progression, but no visual acuity improvement was noticed in majority of the patients. And then came the groundbreaking work of anti-VEGF agents, and they have really revolutionized our treatment for patients with neovascular AMD. We know that ANCHOR and MARINA led to the approval of ranibizumab, followed by VIEW 1 and VIEW 2 for aflibercept, and more recently HAWK and HARRIER studies with brolucizumab with the recent FDA approval last year. These are the approved agents that we have as well as off-label bevacizumab that is also used for treatment of neovascular AMD.

If you look at the data, we know that all of these agents in the trials really led to robust visual acuity gains. ANCHOR and MARINA, obviously we didn't have any treatments, so had observation or PDT. In VIEW 1 and VIEW 2 trials, we had aflibercept every 4 weeks or every 8 weeks compared to monthly ranibizumab, and in HAWK and HARRIER we had aflibercept on-label every 8 weeks after 3 loading doses compared to brolucizumab every 8 or 12 weeks after 3 loading doses. We know that that trial also met the primary end point of noninferiority.

But this is a clear issue here. What we see is that the results we get in randomized clinical trials—as you can see here on the left in terms of visual acuity gains—we cannot mimic those in real world, and you can see that where patients in real world gain 2 to 4 letters, and it depends on the study, we just published a large analysis, a SIERRA-AMD study really showing the same thing, that there are minimal gains in vision, and over time patients lose vision. If you look at the treat-and-extend clinical trials—we're going to talk a little bit about the approach today also—you can see that the gains in those trials are actually pretty good while decreasing the treatment burden. We know—this is the study I was mentioning—that in the real world you have undertreatment which leads to vision loss over time, and really, this sets the stage for need for sustained delivery.

Now, I can tell you that, but how about my colleagues? And this is the PAT survey from American Society of Retina Specialists, and you can see in 2018 the top unmet needs were reduce the treatment burden. Seventy-three percent of retina specialists said that we need agents to decrease treatment burden for patients—and we're going to hear from our patient here today and have a discussion about that—as well as need for longer-acting agents or sustained delivery systems, and 50% of retina specialists said that there is really a need for longer-acting therapeutic options for our patients with neovascular AMD.

Dante, as you saw, that ASRS PAT survey really showed most of us are looking for longer-acting and sustained delivery systems and

also reducing the treatment burden. What is your experience with your patients? What do they tell you about what is their biggest burden when getting treatment for neovascular AMD?

Dr. Pieramici:
Yeah, I think my experience is pretty similar to my colleagues in that I think we've got great treatments. These anti-VEGF agents have really made all the difference in the world, but over time it becomes burdensome. I think it's rough on the patients, it's rough on the medical practice, and it's rough on the patients' families too because many of them are bringing them to their appointments.

Dr. Khanani:
No, I think those are great points, Dante. I think the injection fatigue is real for patients, and we are lucky to have Doreen with us today. Doreen has been my patient for last—over 6 years now— and I'll tell you, she's one of the most compliant patients I've ever seen, and for that reason her visual acuity is actually 20/20 in both eyes. So welcome, Doreen.

Doreen:
Thank you for having me.

Dr. Khanani:
No, thank you for your time. And Dante and I are really excited to have you join us. So, Doreen, tell us about when you got diagnosed with neovascular AMD and how it affected you. And I know you also have a friend who has the disease, so tell us a little bit about that and how you took it and what really it means to have this disease and living with it.

Doreen:
Well, I went in to see the doctor for cataracts, and of course that's—I wasn't concerned about having cataract surgery—but anyway, he's looking in my eyes, and he's dictating to his assistant, and he says, "macular." And I think my heart stopped. And then he looked in my other eye, and he said it again, and I said, "What are you saying?" and he said, "Well," he said, "I can't do anything about your cataracts until you see Dr. Khanani." I was in a state of shock. Luckily, I got in to see you the next morning. And you are wonderful because you saw that I was a mess—I think I cried all night—and you said, "You're gonna be fine. You're gonna be fine. You're not gonna go blind. We have treatments." Because I have a dear friend who was a neighbor, and she's in her 90s, and unfortunately, she got macular before the injections were around, and so she pretty much is blind. I mean, when I go visit her, she says she can see my hands in my lap, and that's about it, and so that's all... I thought that's what was going to happen to me. So anyway, I've been seeing you for close to 7 years, and my vision is still good, and I guess the real burden is coming to see you. I went every month at the beginning, and then we got it out to 2 months. I think I've gone 3 months before, but pretty much it's 8 to 10 weeks I think is usually what it is.

Dr. Khanani:
Thanks, Doreen. When you talk about burden seeing me, is this having a driver? Is it sitting in my office for 3 hours and seeing me for 30 seconds? What is the real burden? And what is the burden after you get your treatment?

Doreen:
Well, if I get both eyes done the same day, no, I'm not going to drive home, so I do have to have a driver. The wait time is long. And now with COVID, you know, there's not room for everybody to sit in the waiting room, so that's a little worse, but I don't know. You know, this is what I tell my friends. It's not pleasant to get an injection in your eye, it's not pleasant for a few hours after because you really can't see very well and do much, and it's not pleasant to sit in your office for hours. But, do you know what? It is what it is. I will do it so I don't go blind.

Dr. Khanani:
So, who brings you in, Doreen, if you're getting both eyes? I know your granddaughter sometime and some friends, right? There's also a burden on the family from this disease.

Doreen:
Oh, yeah. Yeah, I always have to check. Like the friend who was just here helping me get all this set up, she's taken me many times, and my granddaughter, but now she can't do that anymore. And, you know, I've left my car there too, driven myself there and then left my car there, and somebody picks me up, and then we go back and get my car later, but, I mean, I've been lucky because if I call somebody and say, "Are you free to do this?" and then they go shopping or whatever for a couple hours and then come back and get me.

Dr. Pieramici:
After having an injection in both eyes, it probably affects your day the rest of that day, and some of my patients will say it even affects them the next day or 2 or 3 depending on some cases, so I was just wondering about your experience.

Doreen:
No, both eyes is definitely worse than one eye at a time, but the problem is that do I want to go back more often for all this sitting there, so I try to get both of them done at the same time. I never have a problem the next day. It's usually a couple of hours that I really can't see. I can't read or watch TV or anything like that. And then sometimes it hurts a little bit after, but I'm always fine by the next day.

Dr. Pieramici:
Wonderful. You get a gold star. You get a gold star and good vision.

Dr. Khanani:
Thanks, Doreen. Now we're going to have Dr. Dante Pieramici talk about current treatment burden reduction strategies. Thanks, Dante.

Dr. Pieramici:
Arshad, thank you very much for including me in this. I think that, as we've talked about, anti-VEGF therapies have been great, and since we've been using them—probably we first used bevacizumab on a mass basis, but ranibizumab, brolucizumab, aflibercept have made a huge difference for our patients. And initially I think that we were just happy to have such great results, but over time we've seen that patients tend to fail to get treatment as we would recommend in the long-term for various reasons, and one of them being the burden of therapy and that visual acuity can decrease as a result of not getting enough treatment. It can decrease for other reasons too. Certainly, the atrophy can progress, the disease can progress despite good therapy, but burden of therapy and lack of following through with therapy seems to be a big reason for some patients.

So, as typical retina specialists that we are, the clinical trials had very regimented treatment strategies, but we initially right away began to look at other strategies to try to reduce treatment burden on patients, extend the durability of therapy for our patients. You'll find that most physicians are using this treat-and-extend therapy strategy, and there's been a number of clinical trials that have looked at this as well, but there are patients in these studies somewhere between, say, 20% and 60% of the patients actually being able to be extended to a 12-week interval. And, Arshad, I'd be curious to know from your experience. There's a whole spectrum of therapies that are needed if you're using a PRN strategy. Have you seen this in your patients as well?

Dr. Khanani:
Yeah, exactly, Dante. I think we learned from the HARBOR trial, and then on a daily basis in our clinical practice we see that patients need individualized treatment, and I would say a third of patients are still around every 4 to 6 weeks, a third maybe 6 to 8 weeks in my practice, and then a third can probably go more than 8 weeks.

Dr. Pieramici:
Initially, I think that we've really used retinal thickness, fluid in the retina, fluid under the retina, the size of pigment epithelial detachments as a goal. Our goal has always been to get rid of all this fluid because that was an indication of disease activity, and that having fluid in these compartments meant that we hadn't completely stopped the disease. I think that there has been a real shift in how we think about neovascular AMD, and I think of it now as a process that is somewhat physiologic in the fact that for some reason it may be ischemia, it may be the buildup of drusen. There is an ingrowth or a signaling for an ingrowth of new blood vessels, and these new blood vessels in many cases may be providing nutrients—oxygen, glucose and other things to the RPE and photoreceptors—and so there may be a benefit in some cases, and we see these cases of nonexudative AMD patients with pigment epithelial detachments. We know there are neovascular vessels there, and it seems like, perhaps, this is maintaining the eye in these cases, nourishing the photoreceptors and RPE, and so all fluid may not be bad, and we've learned this more recently. We've also learned that different types of fluid can really have different clinical implications.

And to summarize, I think when there is fluid in the retina, cystic fluid, thickening of the retina, the neurosensory retina, we generally want to treat that, and we'll look at some of the data for that. So this was some data here, post hoc analysis of the CATT, the VIEW trial and HARBOR trial, which really looked at subretinal fluid and intraretinal fluid, and we can see in these trials that intraretinal fluid, when there was more intraretinal fluid, particularly when it was in the fovea, there was a reduction in visual outcomes. Subretinal fluid was just the opposite. Subretinal fluid was correlated with better visual acuity.

This is some data here as well from the HARBOR trial. Again, persistent intraretinal fluid was inversely correlated with visual acuity. One of the other things that's come out recently is that fluctuation in fluid. Patients that have more fluctuations in their fluid over time seem to have worse visual outcomes, and we've seen this in the CATT and IVAN trial and the HAWK and HARRIER and the CEDAR and SEQUOIA data.

This is a grouping of all this data here, the CATT, the HAWK and HARRIER, CEDAR, SEQUOIA data, and you can see that these are by quartiles, and the larger fourth quartile are the patients with the larger amounts of fluid fluctuation. And this is a change in best

corrected visual acuity, and you can see that in all these trials there is a diminution when there is more fluctuation in fluid. So again, not only do we want to have therapy that can be extended for our patients to reduce the burden, but there may be a benefit here as well if there's not so much fluctuation in the treatment itself but more of a sustained, continuous therapy.

Doreen, I'd be interested from your standpoint in what treatment strategies that Dr. Khanani has done with you as far as have you been treated every month? or do you come in every 6 weeks? or has it changed over time? What's been your experience, Doreen?

Doreen:
Yeah, it has changed over time. I have been able to go several weeks sometimes. Like I said, when I started out it was every month, but it's not every month now. I would say I think it's been 8 or maybe 9 weeks now since I've been there, so I don't know what it's going to look like next week. But, do you know what? If you could come out with something where we didn't have to come in as often, that would be great.

Dr. Pieramici:
And that, I think, is what we're going to discuss in the next few sections.

Doreen:
Super. I'll be all ears.

Dr. Khanani:
So, Doreen... Dante, Doreen was on monthly, and then she gets bilateral, so I think one of her eyes can go a little bit longer, but I think just for timing we are between 6 and 8 weeks. As you heard, she doesn't really want to come see me anymore. I feel sad about that, so I just bring her in between 6 and 8 weeks, and she has done great.

Dr. Pieramici:
What would be an ideal amount of time to go between needing a treatment, do you think, Doreen?

Doreen:
Even if it was every 3 or 4 months, you know, that's only 3 times a year if it was 4 months. Yeah, I mean, 6 months would be heavenly.

Dr. Pieramici:
All right. I'm going to talk about... Or actually, Arshad and I are going to talk about some emergent management strategies that I think can help with the burden, increase the durability of our therapy, and hopefully end up with the same good visual outcomes and anatomical outcomes that we have experienced.

One of the real exciting things that I think is going to be the first major breakthrough as far as durability and reducing treatment burden is going to be the port delivery system with ranibizumab. This is a novel drug delivery, really essentially reservoir. It's a permanent, refillable intraocular implant. We place it surgically in the pars plana, but it can be refilled in the office multiple times, as you see in the diagram down below, and it should allow the continuous delivery of ranibizumab into the vitreous cavity. And it's a simple device. It just follows Fick's law, simple, first-order kinetic diffusion.

The port delivery system was investigated in a phase 2 clinical trial, the LADDER trial, and in this trial it was compared with monthly ranibizumab intravitreally. In the high-dose group, we found very similar visual and anatomical outcomes, but on average, the port delivery system needed refill approximately every 16 months, and about 80% of the patients could go at least 6 months without needing a refill. The device continues to release measurable amounts of ranibizumab out past 18 months, so it correlates well with what we saw anatomically in our patients, but we got similar visual outcomes, so similar visual outcomes in the high-dose group compared to monthly ranibizumab, so much fewer treatments, much fewer refills, but similar visual and anatomical outcomes.

This brought us to the ARCHWAY trial, which was a phase 3 clinical trial to evaluate for noninferiority in equivalence to the port delivery system, the high-dose 100 mg group, once again compared to the standard care, which would be monthly ranibizumab 0.5 mg. Patients were randomized, and the primary outcome was a change in best corrected visual acuity score from baseline averaged over weeks 36 and 40. And certainly a lot of other secondary visual and anatomical and safety outcomes were looked at.

This is the primary endpoint of the port delivery system. The port delivery system in this study was refilled mandated every 6 months, and it was found to be noninferior and equivalent to monthly ranibizumab injections, and you can see this in the graph below. There was an absolute difference of 0.3 letters comparing the ranibizumab group to the PDS high dose refilled every 6 months.

This is the visual outcomes. There was no change between or no difference between the 2 groups, the port delivery system group or the monthly ranibizumab group. I should note that these are not naive patients, naive to anti-VEGF therapy. These are patients that have shown a response to anti-VEGF therapy, and on average, the patients had 5 previous anti-VEGF injections, so they presented in

the study with good baseline visual acuity. On average it was 20/32 in each of the groups, and it was maintained at that high-dose group, so this is a real challenge to identify patients that respond to anti-VEGF therapy, identify them early with a neovascular disease and begin treatment, and you can get very good outcomes. The problem now is going to be maintaining these injections, and the port delivery system may be a way maintaining these great results over many months or years.

Again, this is a surgical procedure. There certainly are some concerns with a surgical procedure. Vitreous hemorrhages occurred only in 5% of the cases. So initially, in the beginning of the LADDER trial, there were a lot of vitreous hemorrhages, and they modified the surgical procedure to have a scleral cutdown and cauterization of the choroid prior to entering, and in that trial they reduced it from 50% to 5%. And going forward now we see in the ARCHWAY trial 5% vitreous hemorrhages, and most of them are quite mild. They all resolved spontaneously, and none of them needed a vitrectomy to treat this.

Cataract rates were similar between the ranibizumab monthly intravitreal group and the PDS group. Conjunctival retractions or erosions can occur. Again, we close this implant with the conjunctiva and Tenons, but in 11 cases there was some retraction, and most of these cases they could be successfully fixed with a flap revision or a partial thickness corneal graft. Endophthalmitis, which is probably the most worrisome complication of a surgical procedure, occurred in 4 cases. Three of these 4 cases were associated with conjunctival retraction, so with meticulous surgical procedure, monitoring for the possibility of retraction and fixing it early, we may be able to mitigate this and reduce this complication.

Most of the patients the vision returned to baseline. One patient had irreversible visual loss. Again, this is a complication we don't want to see. We see it with intravitreal injections, but certainly we want to reduce this, and we've seen that happen with intravitreal injections, and I think we can mitigate this as well. Rhegmatogenous detachments occurred in 2 patients in this trial, and both of the cases were fixed successfully with a vitrectomy, and the patients have continued in the trial and are continuing to get refills. There was 1 case of a dislocation of the implant into the vitreous cavity. It did not result in an open globe. The conjunctiva was still closed over this. It occurred during a refill procedure. We think that the incision initially was made too large. It was successfully retrieved, and the patient's visual acuity was back to baseline.

This is a procedure, surgical procedure I mentioned, is 3.5 mm scleral cutdown. It's a scratch incision that we do. We want to have it very even on the sides. We expose the choroid, and using laser we diathermize this with overlapping burns, particularly in the corners, because we found that this is where the bleeding was coming from in the cases. And then the eye is entered with a 3.2 or slightly smaller keratome. The implant that has been prefilled with ranibizumab is placed in the spot and secured to the sclera. And then the conjunctiva and Tenons are meticulously closed over the implant.

But I do think this is going to help a lot of the patients. It may not be for everyone, Arshad, and I think that some patients may be happy just coming to the office every 3 months rather than having to have a surgical procedure, but I think patients that are needing very frequent injections may benefit quite a bit from this. And most of the patients in the study really were happy with this and preferred this over the intravitreal injections.

Dr. Khanani:
Thanks, Dante, excellent talk about port delivery system, and really, the ARCHWAY data is really exciting in a phase 3 trial getting noninferior and equivalent outcomes with port delivery system versus monthly ranibizumab injections.

I'm going to be reviewing gene therapy trials that are ongoing. Obviously, we have early data, but I think the data from these trials look promising. First, we'll talk about RGX-314 followed by ADVM-022. RGX-314 uses a novel AAV8 vector to deliver a gene for an anti-VEGF Fab, similar to ranibizumab. It is delivered through subretinal surgery. Here you can see a vitrectomy is first performed with induction of posterior vitreous detachment followed by delivery of the drug using a subretinal cannula where a bleb is made for the delivery of RGX-314, and then an air fluid exchange is performed. RGX-314 is currently also ongoing clinical trials using a suprachoroidal approach. RGX-314 phase 1/2 study is ongoing, is fully recruited. It's a dose escalation design looking at 5 different cohorts. Primary end point is clearly obviously safety followed by secondary end points of change in BCVA and CRT. This is a snapshot of the BCVA data. We have data for all 5 cohorts for first year. You can see mainly the visual acuity has been maintained. We have data for the first 3 cohorts for 2 years, and you can see cohort 3 patients have gained 14 letters. In terms of durability, 50% of patients have gone over 2 years in cohort 3 without requiring any rescue injections. In terms of treatment burden, you can see there's a significant decrease in treatment burden. Again, patients in cohort 5, they have a reduction of 85%. In terms of safety, any new treatment safety is crucial. RGX-314 has been well-tolerated across all doses. No serious treatment-emergent adverse events have been seen in this study. There have been no clinically determined immune responses, drug-related ocular inflammation or postsurgical inflammation beyond what is expected from routine surgery.

Let's talk about intravitreal in-office gene therapy. ADVM-022 uses a novel 7M8 vector to deliver gene for aflibercept in the eye using a standard intravitreal approach that we all are used to delivering in clinic, and it is designed for continuous delivery of aflibercept. OPTIC

is ongoing phase 1 study looking at 2 different doses in 4 different cohorts. Cohorts 1 and 4 are high-dose cohorts. Cohorts 2 and 3 are low-dose cohorts. Also, cohort 1 and 2 are using 13-day PO steroid. And the learning from those cohorts led us to a change. We're using 6 weeks of prophylaxis with topical drops in cohort 3 and 4.

In terms of BCVA and CST outcomes, they have been pretty impressive. Patients in cohort 1 have gone median of 72 weeks without any rescue injections, and cohort 2 and 3 required some rescue. In terms of visual acuity, it's been maintained, and so has CST. In terms of safety, again super crucial to look at that. There have been no ADVM-022-related, nonocular adverse events. There have been no deaths and discontinuations. There have been cases of inflammation in some of these patients, and they have been responsive to and manageable with topical eyedrops. Cohort 1 and 2 used 13-day PO steroids, and we learned that some patients needed more treatment, and topical eye drops were introduced in cohort 3 and 4 for 6 weeks, and inflammation has been manageable. In terms of decrease in treatment burden, you can see there's 100% reduction in cohort 1 where not a single patient required rescue. In cohort 2 and 3, there has been 87% reduction.

So, Dante, I know you're enrolled in the gene therapy trials. What are your thoughts on this? Is this real, or this needs more work for us to see if this is going to be an option for our patients?

Dr. Pieramici:
To the first question, yes, I do think this is real, real from the standpoint that it's definitely shown a proof of concept in both of the trials that you've demonstrated. How will this fit in? I don't know yet. I think it's too early to tell. I think we're asking the body to do something a little abnormal to start producing this protein. And on the short-term, it seems pretty safe. We're not getting inflammation. We're not having a lot of complications. But the real test is going to be long-term. What happens to the cells that we transduce that we start making little bio-factories in there?

Dr. Khanani:
No, I agree. I think it's very promising early data, obviously, and we need to have long-term efficacy as well as safety data to see how we can implement gene therapy to treat our patients with neovascular AMD. Now, let's see what Doreen says, Dante, about the port delivery system data you presented and then the gene therapy data that I presented. As a patient, what does this mean to you, Doreen?

Doreen:
Well, it's exciting. It's exciting that people are working on this, and hopefully we can get something like this so we don't have to get the injections all the time because it's just not a pleasant thing to go through.

Dr. Khanani:
These are really exciting times for retinal physicians as well as patients because I think the future is looking really bright with sustained delivery approaches that can decrease treatment burden for patients but also improve long-term visual acuity outcomes and really address the unmet need in patients with neovascular AMD where we see vision loss in the real world.

I want to thank our audience for their time and attention, and I also want to thank Dr. Dante Pieramici as well as our guest Doreen for participating in this activity.