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www.reachmd.com
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(866) 423-7849

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Managing COVID-19 Related Delays In Patients with Neovascular AMD

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Managing COVID-19-Related Delays in Patients with Neovascular AMD," is jointly provided by Global Education Group and iVista Medical Education, and is supported by an independent educational grant from Regeneron Pharmaceuticals, Inc. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Singh:
Hello, and welcome to this roundtable on Managing COVID-19-Related Delays in Patients with Neovascular AMD. I'm your host, and chair and moderator, Rishi Singh, from Cleveland Clinic in Cleveland, Ohio, and I'm joined by my esteemed faculty panel tonight for the discussion. We're gonna have cases and also a live discussion for you tonight. First, our Dr. Dilsher Dhoot, from Santa Barbara Retinal Consultants in California. We're also with Dr. Sophie Bakri – she is from the Mayo Clinic, and Dr. David Eichenbaum – he is from the Retina Vitreous Associates of Florida in St. Petersburg, Florida. Here are faculty disclosures for tonight's program, and here are our learning objectives for today. We're gonna describe how we managed the interruptions that we saw with neovascular AMD treatment during the COVID-19 pandemic – we're still in it. We're trying to recover from it, and we're gonna talk about how we manage these patients as they return to our practices. We're gonna talk about some of the data regarding anti-VEGF durability. There's been a lot of studies out about the ddurable nature of some of the drugs we have, and some of the studies that are supportive of that, and we'll discuss that in further detail. We'll review a lot of this anti-VEGF safety data, because that's of paramount importance, again, given the length of time and our ability to monitor these patients during this time period. And we'll evaluate some future therapies and get some I – advice from our panelists tonight, and what they anticipate are the next greatest drugs in our field for taking care of these patients. This is an activity provided by the Global Education Group and iVista Medical Education and this activity is supported by an independent medical education grant from Regeneron Pharmaceuticals. For tonight's program – this is a live program – we are broadcasting this, and we would love to take your questions. There's a chat box at the bottom of the screen. Please feel free to enter comments, and we're happy to answer them during this entirety of the program. So, let's start off with some group discussion I have my panelists here, all ready to go. And we'll talk about some of the most recent data that has come out after this pandemic. This was actually some work by the Commonwealth Fund that looked at all the subspecialties in medicine and their outpatient visits, and found that ophthalmology was the hardest hit specialty of all of the outpatient medicine, with a – somewhere between a 75-76% reduction in their outpatient visits. And you can see they – the graph on the right, showing you the number of outpatient visits over time. And I just wanted to – to ask the panelists, just – we can go around and ask each person what sort of delays they've seen of is this graph really equate to what you saw in practice? I mean, this is all of ophthalmology, so I wonder in retina, you saw this same sort of delays. So why don't we start off with Dilsher why don't you tell us about what you observed in the time?

Dr. Dhoot:
Yeah, sure. Thanks, Rishi, for having me. I would say our volume was cut by 50%, but within that, there are subsets, right? I feel like the neovascular AMD population was more likely to show up than say, my BME population during this period, or especially the routine patients who we were delaying ourselves. But I found that, you know, those patients with neovascular AMD were more likely to show up, but there certainly were a number of patients that did delay their care.

Dr. Singh:
David, how about you? How did things go in Florida? I know you had a spike in the pandemic, probably later than maybe most did, but then you also maybe had a different experience with this?

Dr. Eichenbaum:
Yeah, thank you for including me, Rishi, first of all, with these esteemed panelists. These are some of my friends and very bright people, and I'm happy to be here with you and with our audience. In Florida, we had a different experience than other geographies, and I think this was very regional. I think this was very dependent upon the local social and political and scientific and infective environment. In Florida, we had a mandated cessation of elective medical care, and we had not just proactively rescheduled patients at that point, but a lot of patients who were appropriately nervous and pushed their appointments back. We were very careful not to proactively push out injections for neovascular macular degeneration or diabetic eye disease at our practice. We elected to have all of the intraretinal diseases, like diabetes and retinal vein occlusion, continue to come in for probable shots, and neovascular macular degeneration patients come in, but we pushed a lot of other patients out, which was actually met with a lot of resistance. We had about six or eight weeks where we were down between 40 and 45%, and another six to eight weeks where we were down about a third, year over year, compared to 2019. Things are returning to normal, but we're seeing fluctuations in mask orders, fluctuations in infection rates, fluctuations in positivity percentages that may drive us back down again, in the coming cooler months.

Dr. Singh:
How about Sophie, and Mayo. Did you guys see a spike early, late? Are you in it right now? What's your experience been with patients coming back.

Dr. Bakri:
So I think early on, nobody quite knew what to do, and we had this big question of whether we would have enough PPE for the hospital you know, when you're in sort of an integrated hospital-clinic facility and so we actually reviewed each and every patient chart to try to ascertain the risk of treating versus, you know, pushing them out. For example, monocular patients you know, they would come in, you know, maybe certain conditions we could kinda wait a little bit. So really we have to think about the fact that we were preserving PPE and we needed to learn how to operate safely in a COVID environment. Now we're back to normal, I think yes, I think that there is a another peak now, especially with back to school season, we're seeing a peak more in the younger age groups. But I think we've learned to operate safely in the healthcare environment, so it's business as usual, unless the patients don't want to come in.

Dr. Singh:
That's great. I think you've really epitomized, I think in different parts of the country, how this has affected different people. Let me just show you some data from our lab. Actually we have a center for ophthalmic bioinformatics and one of the things we do is, we love to ask various questions. This is a question we asked about a year ago that has a lot of relevance now, and this was actually a question about how many how often we saw lapses of care in our neovascular AMD patients, and what the treatment effect of this was. And I'll ask you if this sort of resonates with you in this pandemic. So this was actually the average lapse, which was somewhere we said the minimum had to be three months to kind of assess this. And we found a significant proportion of patients actually had a three-month lapse. And you can see, some people even had lapses beyond ten and twelve months, in fact, in some of these cases where they're truly not getting any treatment at all. And one effect that had on the patients actually shown here so here is actually a graph that's a little bit busy, but on the left side you see the mean visual acuity in those patients who did not have a lapse, which is maintained pretty much during the course of the study. And on the bottom, you see those patients who had the lapse, who never really, unfortunately, regained that visual acuity they lost, even after a three-month break in treatment. And on the right side, you can see the central subfield thickness, which obviously increases on the time that elapsed, and on the return, you can see that it's pretty close to being what they would have had if they had continuous treatment. So, prior to the pandemic, Dilsher, how common was it for AMD discontinuation, or sort of, delays or lapses in treatment? And what strategies are you employing now more than ever, to prevent these lapses from occurring?

Dr. Dhoot:
Yeah, I would have thought that it was uncommon to have discontinuation in therapy in this population specifically, just because they are acutely aware of their vision. I think that definitely we did see patients that would lose vision, if they lapsed and sometimes they would lapse for different reasons, you know, other life would happen and things they would be hospitalized or there would be some sort of reason for why they might lapse. You know, currently the strategies I employ really are education you know, I guess maybe fair a little bit of fair helps, you know, to try to keep that vision. And so, you know, I try and educate with the with the you know, CT, I think the images are very helpful and powerful for the patients. And really, you have to take everything you have to get their buy-in, and most of these patients do have buy-in, though, because they notice that their vision is improving. And so that's really you know, education and imaging is really helpful, I think, for buy-in.

Dr. Singh:
Yeah. Sophie, I know you have a unique model of care at the Mayo Clinic, where you have injection-only clinics. Was this a commonality where you saw some discontinuation prior? And what happened during the pandemic, and how did you strategize to get those patients back into treatment?

Dr. Bakri:
Yeah. I think you know, prior to the pandemic, you know, the nice thing about having an injection-only clinic is that it's very well-managed. You know, in terms of cancellations, we hear about them, we reschedule. Patients have an option of many days where they could reschedule, so I guess it was less common. You know, we have ways of kind of tracking the patients to make sure that they get the care that they need. You know, post-pandemic, a lot of it was us cancelling, a lot of it was patients cancelling, and then we have to think about those nursing home patients, who are quarantined, you know, for 14 days after leaving the nursing home. And some will get bilaterals, but there are some who refuse to get bilateral same-day injections, because they find them uncomfortable, so then they're quarantined all month. So, there were there was some resistance from patients to come in as well.

Dr. Singh:
How about you, David? How did you encourage patients to return back to clinic despite all the nursing home related issues, and the other complexities around this?

Dr. Eichenbaum:
So, similar to Sophie, we have a lot of injection-only visits. We have basically three kinds of visits for the macular degeneration patients: dilation, imaging and injection; imaging and injection; and injection only. And what we did to keep the patients coming in is we converted a lot of them to injection only, in and out, visits. And we actually added a fourth kind of visit for patients who were ill, or COVID positive, or contacted with COVID-positive people, which were express injection-only visits, without a vision and without a pressure. And we told the patients we would get them in and out quickly. We converted more of them to these rapid visits, and we had these express visits, and we were also acutely aware of drop-off as we'll talk about in the cases later. You know, we probably have drop-off all the time I think all of us do and we all have different ways to track that in our practices, and recall patients, and try to bring them back in, some probably better than others. But I think we were very aware of it in this period. And we see, in clinical practice, what you saw in your lab study that the patients can get anatomically better after a lapse or an interruption of treatment, but oftentimes there's irreversible vision loss.

Dr. Singh:
Yeah. And this is a great question from somebody watching the roundtable tonight, asking about what there is in the horizon, or even now with regards to remote monitoring. So, were you able to use any tools that might be helpful to people for remote monitoring, and what do you think the promise of these devices might be in the future? How about why don't we start with Sophie?

Dr. Bakri:
So, in terms of, you know, home monitoring at the most basic, you know, we know that the there's the newspaper and there's the Amsler grid. And then, you know as we get more sophisticated, there are there is the the Amsler grid by Notal Vision the home monitoring system. And then, as we get even more sophisticated, the there are home OCTs being developed. Now, the question is how will they all integrate, and then what's the model for who gets the alert, who contacts the patient, is it real, etc. I think these are things that many of us are trying to figure out you know, our practices, because, you know, there can be false alerts, there can be real alerts, but these are definitely ways that I think we can refine and use more of in our practices, especially now.

Dr. Singh:
Mm-hm. Yeah, one of the ways that we did it at the Cleveland Clinic was I guess a sort of a hybrid visit model, which was what we had as the patient would come into the front door, get a vision, an OCT, and that was it. They actually left at that point. That was another way we sort of integrated, without doing home OCT, but we were able to at least interpret the images and get a sense of what was going on. David or Dilsher, did you employ any other, sort of, strategies for monitoring the patients at home, whether it be nursing call-backs, or something else that was helpful at this given stage? Or do you see something on the horizon that excites you about home monitoring?

Dr. Eichenbaum:
Well, we know we have the Notal device in registration trials now, looking at home OCT with artificial intelligence-powered reading of the home OCT. We know we have that coming. We know that we don't have anything right now that's validated or approved for neovascular macular degeneration at home, but I think there's a lot of promise in home OCT, if the cost can be mitigated and the patient's image acquisition or, kind of finding a baseline to use a 4C home term and be mitigated, compared to the poorer results we see with the existing intermediate dry macular degeneration device. But we did not do anything novel for home monitoring because we

didn't believe that there is anything for that. I think the hybrid visits that you employed are the closest thing we have, which are sort of express imaging visits.

Dr. Dhoot:
And we were very similar to David we there is really nothing novel but I do agree with him that home OCT does excite me. It's certainly an area able to develop a machine that can be deployed to, you know, the masses. It will be very good for our patients.

Dr. Singh:
So, I have put up this slide just to talk about fluid, and just to kind of gauge your responses to this, and see what your thoughts were on this when you saw patients. So, you know, you have these patients who have various compartments of fluid. Obviously, we know that there are certain compartments that are worse than others. Some compartments we don't even know what they mean right now, probably sub-RPE fluid falls into that category. And I wonder with your treatments and deciding about regimens and treat-and-extend. Were you trying to be aggressive with treatment during this pandemic? Were you saying, "Okay, well, subretinal fluid's there, I'm still gonna extend them."? Or, "I'm gonna do, you know, a little bit of more of a continuation of their current regimen." Walk me through, kind of, Dilsher, how you looked at thesecompartments and decided about treatment and regimens for recurrence of those treat-and-extend regimens.

Dr. Dhoot:
Sure, I generally agree with everything on this slide, and so subretinal fluid can be something I'll tolerate some amount of. So this bout of retinal fluid was more perhaps more apt to extend during COVID than prior. But it was extending prior to COVID, too. I remained intolerant of intraretinal fluid during COVID, and so I would keep those patients on strict intervals and not extend if I saw any intraretinal fluid. And sub-RPE fluid to me, it really doesn't enter into my treatment paradigm. And so, yeah hopefully that answers your question.

Dr. Singh:
Yeah. How about how about Sophie? Anything here was it a zero tolerance for fluid or were you a little bit more labile or lax because of the situation we were under, and continuing now into

Dr. Bakri:
I think it really depended on the vision as well, and on the state of the other eye, and on the general health. You know, we are looking also at systemic risk factors and age for people coming in. But, to answer your question about fluid I mean, intraretinal fluid is the most serious when it comes to affecting vision. We tolerate PEBs, we tolerate a little subretinal fluid.

Dr. Singh:
And, same question for David before we go on.

Dr. Eichenbaum:
Yeah, so my goal and this is a treatment naive patient my incoming goal is always treat to dry, right? We all wanna treat to dry, and 90+% of American retina specialists are treatment extenders, so what I would do during the pandemic is when we were extending a patient would come back with subretinal fluid. I probably even have further relaxed my pre-pandemic predilection to allow it to exist. I have probably said, you know I'm not gonna bring you back sooner. And I'm probably gonna stick with that, because there is good data supporting it, and it kind of seems to be working from the seat of the pants, so to speak. But my default is treat to dry. I now tolerate a small amount of subretinal fluid, but I won't extend the setting of subretinal fluid like some treat-and-extend trials do.

Dr. Singh:
So, you know, we have a lot of different dosing regimens I just put up the slide for everyone to see, you know, really that we've all sort of settled on treat-and-extend, but we obviously have monthly data, we have bimonthly data, we have PRN data, we even have quarterly data on some patients. Tell me about when you saw a patient during this time period right now, where we're in, Dilsher, and how you were able to continue them. Were they all treat-and-extend? Did you have to go to monthly on some of them, or did you sort of say, Well, you know, I we can only see you so often, so we're gonna go quarterly? Talk to me about how you reinitiated this patient when they came back to you after maybe a delay in care.

Dr. Dhoot:
Yeah, they came back after delaying care and they were surprisingly stable. And so, for example, if I was treating them every six or eight weeks, and they were dry, they were starting be extended and they self-extended to say, three or four months, and they were stable, I would keep them at that interval. So I would keep them at three or four months. They came back and they were worse then I would go back to monthly and I would restart the treat-and-extend paradigm treating with the goal of having anatomic dryness. And so that was kind of so it was very much customized to the patient and what they did following the lapsing period.

Dr. Singh:

Sophie, a patient comes back, they have been on treat-and-extend for let's say ten or twelve weeks, they missed three visits or two visits with you. What are you doing with them if they have a lot of fluid on their OCT? Are you backing off? Are you going right back to their regular interval? How are you handling that patient?

Dr. Bakri:
So in other words, if they were at if they were at twelve weeks dry, but then they missed six to nine months' worth of treatment…

Dr. Singh:
Sure, absolutely, yup.

Dr. Bakri:
Yeah, so really, whenever someone recurs like that, I start right from the beginning with monthly treatments, to just dry them out again, and I start the treat-and-extend cycle all over again.

I know I'm conservative, but at the end of the day, I think it's a more aggressive approach is more likely to restore lost vision.

Dr. Singh:
Right. How about you, David? What were you doing with these patients, when they came back with none?

Dr. Eichenbaum:
I agree with Sophie. We had a number of patients who came back, instead of at an eight- or ten-week interval, they come back at four months or five months, and they have fluid, and then we treat them aggressively. We treat them like a treatment-naïve patient that's for the most part at least that's what I do in my patients in the practice. And we can dry 'em out, but we can't always get 'em back. But I tell 'em that we're fighting an uphill battle and we're behind the eight-ball, and I make it relatable, and they buy into it, because they almost always notice that things have changed.

Dr. Singh:
Right. Let me walk you through some data, just to kind of give you a sense of where we think there is evidence for quarterly treatment. And this is actually data from View 1 and View 2, and Year 2 patients, because Pier 2 actually had a PRN sort of area, where they were treating patients on an as-needed basis for the 2$^{nd}$ year with giving them quarterly interval injections as a booster. And they found that almost 50% – 44-48% of patients were able to maintain on that regimen of essentially quarterly treatments after the first year. Then you had ALTAIR, which is a nice study done in Japanese patients, but has a lot of relevance to our neovascular AMD patients here, because they did do a nice evaluation of the definitions of treat-and-extend, and they extended by either two-week or four-week intervals, which I think was an interesting paradigm. Whether you need to be so cautious and extend by a week or two weeks, or even four weeks they were testing that in that study. And they found, again very equivalent gains in visual acuity when you extended either two weeks or four weeks, and again, validating treat-and-extend as a valid regimen of treating these patients, with a good number of patients able to go beyond a quarterly injection. In fact, these patients actually went up to every-four-month injections. You can see, almost 56.9% of patients in the in one arm and 60% in the other arm, actually were able to go twelve weeks and beyond in these studies, which I think was quite impressive data. And then we had ARIES, which looked again, sort of at that ability to hammer patients early with a more frequent treatment, and then look at treat-and-extend early versus late, and see if there was a difference in the final outcome. And what ARIES essentially found is there was no difference in those patients who had early versus late treat-and-extend. But again, a high number of patients with a very durable treatment here which you can see, of greater than three to four months, in a vast majority of people. And I'll finish up with this last data point, which is the HAWK and HARRIER trials, which again showed you there are other drugs that are available just to be fair and balanced, that have abilities to dose with 50% or more at year one and Q12. Now looking at all this together, I want you all to comment, sort of on which drugs you think have been durable in your hands. Is this what you're seeing in practice? Are you getting quarterly treatments with your patients? Why don't we start with Dilsher. Is this something you've that resonates with you, this data seeing 50% of patients get quarterly and are you do you feel like it's drug-dependent or you feel like all drugs are the same for that matter?

Dr. Dhoot:
You know, so I think that there is a large proportion of patients can get to quarterly dosing. I do think that there's some drug dependence there. I don't know that it's 50% in my hands, I feel like it's probably closer to 30 maybe even 25% of patients that we can get up to quarterly dosing. I feel I mean, just based on my anecdotal experience, I feel like bevacizumab is not as durable. Aflibercept probably has a little edge over ranibizumab, but they're very close. And you know, brolucizumab is similar to aflibercept in my opinion. And so, I think that it really just there are patients, though, out there that, you know, don't require, you know, the dosing and they can even be extended with bevacizumab, but it just speaks to the heterogeneity of the disease. But definitely we do have these patients.

Dr. Singh:

Yeah, great point. How about Sophie? Sophie, you have this injection-only clinic. Are you were you getting a lot of patients able to go quarterly? And what drug were you finding that in, or was it just all drugs were the same?

Dr. Bakri:
I have plenty of patients who can go quarterly, or you know, ten to twelve weeks. And I think the proportion is higher with aflibercept than bevacizumab, but I do have patients on bevacizumab and also ranibizumab who can get out that far. So some of it will be the drug, but some of it will be the aggressiveness of the disease.

So, yeah. It happens, and is it 50%? Not quite, maybe more like Dilsher's experience, I think, of 25%.

Dr. Singh:
Yeah. David how about you? You know we talk about these drugs, and BEOVU is out there right now for you to use what's your perception around usage of that in comparison to aflibercept, or ranibizumab, or even bevacizumab, at this given stage?

Dr. Eichenbaum:
Yeah, you know there was an old presentation I did a couple of years ago, where I talked about how it was the patient, and not the agent. And I think in a large proportion of people, that's true. Like Sophie said, on bevacizumab, ranibizumab, aflibercept or brolucizumab, I have a goodly number of patients, I think approaching this data at quarterly dosing. The individual response to drugs, though, is very real, right? And I was very avid about brolucizumab at launch. I used a ton of it at launch. I was an investigator in the registration studies, and all of us have backed off on the frequency of use, in probably treatment-naïve patients, because of the problems related to intraocular inflammation. But I do think that there's probably something to different agents in different patients. And I do see some differentiation, especially in the more aggressive biology. The patients who have worse pathophysiology seem to have some individuality, typically favoring aflibercept or brolucizumab, over ranibizumab or bevacizumab, but not always. And I think individualization is key, and I'm happy we have a slightly larger toolbox, albeit with the same type of tool, with the addition of brolucizumab.

Dr. Singh:
Dilsher, have you backed off of BEOVU at this point brolucizumab, given this? Or have you experienced these inflammation issues and is this just a brolucizumab thing or do other drugs have inflammation issues as well, and have you had to deal with those too?

Dr. Dhoot:
Yeah, so I have backed off. Like David you know, coming out of the gates I did use a fair amount. The inflammation is concerning. I think it's a real number, and the fact that if you are a patient, you know you end up the majority of patients regain their vision, but you know, if you have a this type of vasculitis, you're not regaining vision, so it's quite scary. Fortunately, I didn't have any of those patients but because of the cases that we've seen I have backed off especially in treatment-naïve patients. There is still a handful of patients actually that insist on receiving it, and as long as they understand the risks, I'm okay with using it. And so, as far as other drugs with inflammation, you know, we are all aware of the the inflammation that we saw with aflibercept, and these kind of were discreet time points in the I in the past few years that we've seen these spikes. You know, fortunately, those are were mild, and very much treatable, and we and I did not see, you know, vision loss, so it has been easy to tolerate that. And fortunately, we don't have those issues currently, and hopefully it won't spike again.

Dr. Singh:
Yeah. Very that's good comments. So let's show this last slide, before we get to the cases, and I just want to gauge, you know, we obviously we're challenged right now to come up with something better. We have drugs that last, you know, maybe three months, maybe four months – that's probably not enough. But we have a lot that's going on with regards to clinical studies. We have high-dose anti-VEGF treatments, as you know. Regeneron is involved in a few of those. We have, obviously, some gene therapy studies, which I list as moonshots, but I guess they're becoming more like reality than moonshots are given this time. We have ANG2 and other biological targets that are being looked at VEGF C and D for example that's being looked at for targeting in these kind of categories. And finally, for delivery or extended-release sort of, devices. So if you had to look at these together Sophie, what's to you is the most exciting and what are you most interested in using when it comes out? Let's put it that way.

Dr. Bakri:
Okay, so the most exciting, I think, is gene therapy. If it truly is a one-shot deal, I mean, that's a real game-changer. I think second most exciting would be the port delivery system.

You know, if we can go 14 to 16 months between refills, I mean that would be just fantastic. And then I think you know, the ANG2 you know, it's all about durability. I mean, give me something that's a one-shot deal great. Now, in all of this, we obviously have to consider safe like safety, you know, inflammation, infection rate, etc., and so hopefully they all get approved and hopefully they're all safe and

efficacious, and we'll be in great shape.

Dr. Singh:
Yeah. David you look at these and they're just such a promising field of various applications here that could exist. What do you think is gonna change the lives of your patients the most?

Dr. Eichenbaum:
So I love this slide this is a great slide. This is a lot of fun. This is the stuff that we're in it for, because even though we talk about how retina's developing, innovative, enlightening, in a bottle we basically have been doing the same thing commercially in the real world for 15 years, and all of these give us a chance to do something different, to some degree. Of all the things on this slide, if I had to lay my nickel down on one that I wish was available commercially right now that has good safety and efficacy evidence so far, and I wish I had it during this pandemic, it would be the port delivery system. It we've been involved with that since Phase II. Yes, it does have its share of things that we need to overcome to make it sort of the gold standard treatment. But the Phase III archway results and the endo-study LADDER results are very promising and my port delivery patients are very happy during this pandemic, and I'm very happy that the vast majority of them are doing well

Dr. Singh:
That's great. Dilsher, how about you? What do you think is putting your nickel down on something? What do you think is the most promising of these that is gonna change the outcome of your patients?

Dr. Dhoot:
I agree with David. I'm really excited about port delivery, partly because it's at the finish line now, and so, you know, this is something that's in that's very close to being introduced to our patients and I'm excited about the durability aspect of it. You know, gene therapy excites me. It's relatively early if they can deal with the inflammation issues and I think that gene therapy would be amazing. It's a moonshot, but I think it would be something that would really be a gamechanger. The one thing about all these therapies though they address the unmet need of durability, unfortunately we don't see you know, vision improvements, you know above and beyond, you know, standard of care currently, and that really still remains an unmet need for these patients.

Dr. Singh:
Yeah, that's a great point. I think that obviously, there are patients that come in with a certain level of vision and just maintain that vision, and there's not much we have for them right now. It's a really great point. So let's talk about these cases that you all provided. I love these cases. So if you I'll advance the slides for you, and you can talk us through this case, and we can learn about this.

Dr. Bakri:
Great. Thank you Rishi. So this was an 83-year-old female with wet AMD in the right eye. She has 20/30 vision. Left eye was dry, but I included it. She's just got a small PED in the left eye. And, the OCT pre-treatment in the right eye was 20/30, so it's pretty good, but there was intraretinal fluid and there was a little bit of subretinal fluid and some PEDs. So, to cut a long story short, she received nine monthly injections of anti-VEGF therapy in that right eye all bevacizumab and then tried aflibercept injections. She was 20/40 the intraretinal fluid had resolved, but she still had some subretinal fluid. And she was supposed to come back in one month, because she was on monthly anti-VEGF therapy, but due to COVID-19, she ended up having to skip that one month of treatments. So, just after skipping one month of treatments, or two months after the last anti-VEGF injection, her vision declined dramatically, from 20/25 to 20/200. Now you can see a lot of intraretinal fluid, subretinal fluid and much larger pigment epithelial detachments. So we started again monthly, went back to monthly aflibercept, and after four injections, vision was 20/150, and pretreatment, her vision was 20/30, so she she had a large decline in vision, just by skipping one month of treatment, and it was never regained back.

Dr. Singh:
That's a sad, sad story to see that. So, looking at her initial lesion, you said that her initial lesion was an occult lesion? Or was it a classic lesion on her her angiogram, or?

Dr. Bakri:
I think it was like a minimally classic lesion, but if you go back, we can certainly take a look at that. Yeah, so you we only see one frame. There's a little bit of increased hyper fluorescence there –

Dr. Singh:
Yeah, maybe…

Dr. Bakri:
Right there, right. So maybe it was minimally classic.

Dr. Singh:
Yeah.

Dr. Bakri:
And that would go along with having a PED, intraretinal fluid and subretinal fluid.

Dr. Singh:
Yeah. Yeah, I don't know how much this maybe plays into it. Maybe that's a great research project, to look at, sort of the lesion type and its delay, and what that what meant, but it's interesting. I don't know how people really get angiograms reliably. I'm glad you got it, because it's helpful to see this, and see its aspects. So, what were you what are you thinking about this patient now, given that fact that you had these four injections now, and you have this almost like double layer sign, I guess you could call it. Is that what you'd call a double layer sign present, right here? And on top of that, you have some intraretinal fluid present, so what are your thoughts on the prognosis for this patient, or their or continued therapy?

Dr. Bakri:
So I think this is clearly one of those patients that's really dependent on monthly anti-VEGF therapy. As it stands, you know, right now because of the COVID pandemic, I didn't want to switch to brolucizumab, because, of course, of concerns about, you know, inflammation. And so, really the only option that we had aside from that would be to continue monthly, you know, aflibercept. Now, could we be doing injections and alternating, you know, every two weeks? That's certainly something that's discussed. But we didn't do that, and definitely, you know, these are sort of "out of the box" methods. But I think we gained quite a bit in terms of the OCT, and you know, hopefully we continue to make make more visual gains.

That parallels the OCT gains.

Dr. Singh:
Any comments from the panelists on what you'd do with this patient, given this sort of level of vision and what's happening? David, you were about to say something?

Dr. Eichenbaum:
I was gonna say, purely interesting thing is first of all, Sophie, the patient, when the recurrence occurred, looks worse than we had anatomy at any other point. I don't think we had a baseline OCT, but it looked really bad, right? That…

Dr. Bakri:
We do have a baseline OCT, David, and you're absolutely right. Pre-treatment, pre-any treatment, 20/30, with just a little fluid. And I had never really seen this massive rebound like that. Good point.

Dr. Eichenbaum:
Yeah, really, really interesting. And the second thing is more of a question than a comment. Would you put a port in this patient? Or do you think the VEGF load is too great?

Dr. Bakri:
I would…if I had a port, I would put a port in this patient. This is an ideal patient for the port delivery system. Somebody who's dependent on monthly therapy, and demonstrated to have that dependence.

I wish we had it right now.

Dr. Singh:
Yeah. Dilsher, any comments about this case? Have you seen something like this before? What's the, kind of, outcome of this sort of situation?

Dr. Dhoot:
Yeah, fortunately, this case is rather atypical. I mean, this is a minority of patients that require, you know, monthly injections to start with. And then to have this rebound after just one month, is really unfortunate for this patient. You know, I would do exactly what Sophie's doing. I would be injecting this patient monthly with aflibercept but it yeah, I would also put a port in this patient to have some baseline anti-VEGF, and I probably would top off with you know, injections on top of that, if the patient need be.

Dr. Singh:
Great. Okay. Let's go on to Dilsher's case. Dilsher, here is your case.

Dr. Dhoot:
Yeah, thanks. So this is a patient of mine that I think our point is so let's see here so this is a 70-year-old female, with a history of

neovascular AMD. She was referred for her CMV back in 2016 in her left eye. And she received an anti-VEGF about every 5-6 weeks, very faithfully she would return for her appointments. Initially she was treated with bevacizumab for six injections, and due to the persistent fluid, we switched to ranubizumab. We gave her three tries there and still had persistent fluid, and she ended up on aflibercept and she got 25 injections of aflibercept to the current time. There was always persistent subretinal fluid, and we'll see that in the next slide, then. She was lost to follow-up kind of in the middle of the COVID pandemic, you know you know in May 28 until September 1st, so three months she went, rather than her usual six weeks. And so, she went an extra six weeks, and so we'll see how she did. So here's I just for, you know, reference, I showed you 2019 here, and I she had been receiving injections and so you don't have her treatment-naïve OCT. But you see back in January of '19 she had a some trace subretinal fluid. She went six weeks, there's more subretinal fluid, so when she went a little longer, it you'd see, there'd be greater subretinal fluid, and then in April, she went back to about a month, and you see the subretinal fluid improve, but persistent. The trace levels. On the next slide here, we'll see some OCTs from 2020, so we'll fast forward here to March of 2020. So in March of 2020, always a little bit of fluid. You see the PED there. She receives another injection about 5-6 weeks later, in April. And then, the last time I saw her faithfully was May of 2020, again with a little bit of subretinal fluid. And then she disappears, right? She disappears for an extra six weeks and so let's see how she does. So, here she is. So you see, after that extra six weeks, there is more subretinal fluid. Interestingly, her vision is better, right? So she was 20/60, she offered around 20/40 to 20/60 you know, in her 5-6 week intervals. She comes back, you know and she's 20/30 a little bit more subretinal fluid. We treated her with aflibercept and took her back to her six-week intervals.

Dr. Singh:
So I guess the question, Dilsher, when you look at this case, is if the patient is improving sort of spontaneously on their own, are you dealing with a very favorable lesion where you don't, you know, need to treat potentially, I guess is the question? I mean, I know it sounds crazy, but people treat occult lesions all the time, but they don't necessarily need treatment, per se, if you look at the natural history. Do you think you did you have an angiogram? I didn't see the angiogram from the beginning of that patient.

Dr. Dhoot:
You know, I didn't actually have an angiogram for this patient. So, yeah, yeah, you know, you bring up a good point, and so it makes you wonder, right? I mean, we clearly we see that in the when we delay treatment, the fluid does increase, right? And I think everything inside of us wants to treat that fluid, because it's worsening, right? I think if an occult lesion that's stable subretinal fluid, you know, I feel a little more comfortable maybe not treating. But when I see fluid that's increasing it makes me want to treat it, because it is the normal response for most of us. But interestingly, this patient, you know fortunately for her, doesn't lose vision. That's probably another reason why, you know, she could she extended herself in a way, because she wasn't perceiving the symptoms of this increased fluid.

Dr. Singh:
That's great. Any comments from the other panelists about this case? I think it's a great case to kind of illustrate a different outcome with regards to the these patients here.

Dr. Eichenbaum:
So it's a really interesting case, because she does better with the subretinal fluid, like you talk about, and the natural history of the occult lesions, like you were just mentioning. Did you think about keeping her quarterly, Dilsher? I agree I probably wouldn't let her ride, because she came in with symptomatic vision loss at some point, I presume. But I wouldn't necessarily dial her back on the apex, and the fluid is this "healthy fluid" that we discuss a lot in the modern era. Did you think about keeping her at a Q12 interval?

Dr. Dhoot:
That's a good thought. You know, maybe – maybe I'll go for eight weeks next time she comes in, you know, just based on that.

Dr. Singh:
Yeah. Sophie, how would you what do you think your management style would be with this patient, that clearly got better on us on its interesting NEEP finding? What are your thoughts on that?

Dr. Bakri:
Very lucky patient, but I wouldn't push my luck too much.

Dr. Singh:
And what about, Dilsher, the treatment interval here? I think that David brings up a good point. You went back to six weeks but let me tell you let me ask you what you what your thoughts were on continuing at that level of six weeks. Is this something you think you might be a little bit more aggressive in extending as it goes along? Or do you think you're gonna stay this way?

Dr. Dhoot:
Yeah, you know, in thinking about this case now, you know, taking a moment to pause and look at these, and you know, I might later go

to eight weeks. You know, it being since she seems to do okay without we have good data from, you know, B1, B2, it you know, patients at eight weeks can do well with aflibercept, and so I think I probably would, probably go eight weeks next time, knowing that, you know, she can go, you know, three months. But, yeah, I don't know that I would I'm kind of in Sophie's camp I'm a bit conservative.

Dr. Singh:
Yeah. This is a great question from somebody in the audience about just the comment we made before we go on to David's case. About the express visit discussion, and Sophie, you have a clinic that's like this. And they ask, you know, what do you check? Do you check vision, IOP, just the injection? And should it really be the standard of care? Can you comment on that a little bit?

Dr. Bakri:
Okay. So I think "express" is a relative term. Express, to me, means drive-thru. I think it when I say a relative term, in that we are thorough, we do check the visual acuity, we do check intraocular pressure. Remember it's important to also monitor the other eye, and that way we we know if something is occurring as well. So the whole visit would be about 20 minutes, when all of that done, versus a normal visit that involves an OCT or a first visit that involves a fluorescein and an OCT, and a, you know, a long discussion about what macular degeneration is and the treatment options.

So, I'm in the camp that I feel that we should check vision and pressure every time. I know there are different opinions on whether pressure needs to be checked, and now on maybe the "super express" camp, whether we even need to check vision. But I suspect, in the future, with willing patients, we may be able to have people check vision before they come in, on an app, for example. You know, we don't have a way, that I know of, of checking pressure at home yet, but I think as this technology advances we can certainly make progress in that area.

Dr. Singh:
You've done a lot of work on intraocular pressure and anti-VEGF therapy. Can you summarize some of that data for us, so we have a better sense of if there's truly a risk here for glaucoma in these patients?

Dr. Bakri:
So what we found and this was looking one of the studies that we did was the sub-analysis of MARINA and ANCHOR. You know, there's about a 7-10%, 7-10% of patients receiving ranibizumab that will have a pressure rise at some point. Now, pressure rise obviously depends on where the cutoff point is, right? So we have many different endpoints, combinations, etc. But, pressure increases do occur. And before that, we used to think of pressure increases just occurred with steroids.

Dr. Singh:
Right.

Dr. Bakri:
And they actually could go with anti-VEGF therapy, too. And we don't want to miss one of those. Now we still haven't figured out why it occurs, whether it's the result of repeated intravitreal injections and repeated increases in pressure or whether it's a biologic effect.

Dr. Singh:
That's great. This is another great question about that patient from the beginning. In the first case, with rebound activity, do you think the combined use of an anti-VEGF and steroid might be helpful in that patient? You know, we used to use steroid in the PDT era I think that was mainly from the inflammation around the PDT, but is there any value to steroids in these patients at all?

Dr. Bakri:
So, I don't think so. I have tried it, you know, just as we emerged from the PDT era and we had, you know, one anti-VEGF available. I tried it in certain patients, and I mean the literature is out there now. It really doesn't add much, except most steroid-related complications.

So, I don't think so.

Dr. Singh:
Mm-kay. Great. Alright. That's awesome. So, David, we're gonna go on to your case now, and here it is.

Dr. Eichenbaum:
Alright. So this is a case of a guy who I like this patient quite a lot. This is kind of a sad case similar to what we saw with Sophie's patient. This is an 82-year-old monocular male, and he's monocular because he has a fibrotic scar in his fellow eye, and I think that's a biomarker for bad disease. If you got a patient with a fibrotic scar in 2020-2021, that patient has bad disease. Something went wrong, probably during the anti-VEGF era, in the fellow eye. So that means that the remaining eye is probably biologically aggressive, right? So this guy proves that out. This is an 82-year-old guy, and in his good eye, he receives an injection every four to four to five weeks. He

gets aflibercept. He and I have talked about brolucizumab. I frankly don't know if that would be enough to push him out to the eight weeks that you need to continue to have label compliance with brolucizumab as it exists today. He has not elected to try it yet, because he's been happy with high-frequency injections, relatively speaking. Let's go on to the next slide and I've been treating him for years. This is a long-time, and this is how he looks. This is pretty good, when the fellow eye has a fibrotic scar. This is January of 2020. This is kind of his treated baseline. This is what he looks like when he typically comes in. He's a little thin in the inner retina, because he also has advanced glaucoma, possibly, to reflect on Sophie's work from a series of frequent intraocular injections, possibly because he's just a glaucoma patient, maybe a little bit of both. Let's go on to the next slide and he comes in for injection-only visits. These are multiple undilated, with two I's, like Xiidra, injection-only visits. He comes in and he gets injections with vision and pressure, and it's not just because he's a glaucoma patient that I check the pressure. I think it's important to check vision and pressure, in what we consider the "express visit with injection-only visit." And the staff knows that if there are symptoms, especially floaters or a shadow, or a change in the vision, or a significant change in the pressure to a level greater than, you know, 20/22, something like that then the patient flips automatically to a dilated visit. But here he comes in, and that was his January visit, February, March, April. Here is in March he got an OCT with his injection, still at his relative baseline. Let's go on to the next slide and then he misses one visit, because he lives in a facility, and there was a quarantine with travel. He was isolated from his family who brings him, and he was scared of the COVID, because there were people in his facility who got COVID. He comes back two weeks late, and he has dropped to 20/400, and if we look at the next slide, he has a recurrence very similar to Sophie's patient his PED is up, his intraretinal fluid is up, he has a little bit of maybe I don't know if that's real subretinal hyperreflective material but there's something going on in the outer retina, and he returns to frequent injections. He never gets his vision back, though. He remains at a level of about 20/200 today, and I have not subjected him to another OCT by the time I submitted this case, but this is the, the warning, and this is a patient who I would also put a port in, or if we had a safe and effective gene therapy, of course, that would be the dream that's the moonshot. But he would get a port and I would try alternative agents on him if he was willing to do that. If he was willing to go for a brolucizumab today, I would give him one. If he was willing to go for a furisumab tomorrow, assuming it has good safety, efficacy and durability, I would give him one. This is the kind of patient who needs more than we've got today.

Dr. Singh:
That's great, David. A really good case. Sophie, any thoughts on how David should manage this? Or maybe do differently in this patient's situation?

Dr. Bakri:
I mean, I agree with everything David said. I think he's spot on there. But now I'm thinking about a comment that you made earlier, Rishi, about there's certain types of lesions, on fluorescein angiography that we could identify, where you can stop the treatment for awhile, but then we just have recurrence. You know, they recur with a vengeance. And you know, David was this a minimally classic lesion, like the one that that I presented?

Dr. Eichenbaum:
Yeah, so when he first came in, I did get an angiogram on him when he first came in and that he was at minimally I don't know, I can't remember exactly what his classification was, but his acuity wasn't 20/400 with all that CME. He had subretinal fluid, and he had a PED. And it'd be interesting to go back and look, and see what the characteristics were that baseline OCT, three or four years ago, when he first came in with his second eye going down the tubes.

Dr. Bakri:
Well, that's good. We're making scientific progress with an N of two tonight.

Dr. Eichenbaum:
We always do, right? I'm feeling validated.

Dr. Singh:
That's the way good science happens right now, with our current administration. So I think we did pretty well in the whole thing, so. Let's summarize some of the I think the findings from tonight's program. We're sort of hitting the witching hour now. Dilsher, what are your thoughts on sort of giving summaries on, you know, all of these learnings we've had from tonight. Where what do you think patients' outcomes should be? How do you think we should best manage these patients during the pandemic? What would you tell practitioners now, based upon your experience, what you've seen?

Dr. Dhoot:
Yeah, I would say that I still feel strongly that this a very heterogenous disease in population, and we really have to customize what we're doing during the pandemic. I think that, you know, it's fine to try to stretch the limits and extend these patients, but, you know, many of them, as you've seen, you know, require monthly treatments, and so, you know, ultimately you know, we just have to do our

best to keep our offices safe and streamlined, and you know, to take the universal precautions that we are, to keep these patients safe when they visit us, and keep ourselves and our staff safe. But I think that, you know, you can try to stretch the limits a bit, but, you know, it really just depends on the patient.

Dr. Singh:
Sophie, any comments about, you know, you look at these patients now, and they come back. What are you're so well-versed, and you've done so much clinical trial work, what do you think is the best way to take care of them when they've returned to you as you as you've done them right now in your clinic?

Dr. Bakri:
So, I mean, I think it's very clear tonight. We identified a group of patients who depend on very frequent anti-VEGF therapy. They, in fact, do well on anti-VEGF therapy. But they're dependent on it. I think those are the exact patients that we want to use a port delivery system in, or down the line, you know, gene therapy. We know what happens now, when we stop. I mean, COVID is a horrible thing, it really is. But it's taught us a lot, and taught us, I think, how I think we've all learned more about the management of our patients, because, let's face it, we very, very would rarely would stop treatments.

Dr. Singh:
And David, what do you think about you know, your learnings from the pandemic, if you're gonna apply these hopefully not for another spike, but in the future. What are what are your thoughts on what you've learned so far?

Dr. Eichenbaum:
So, a couple of things. We've gotta balance what we know that there's a correlation between injection frequency and seeing better in neovascular macular degeneration. But, we have all of this data on how a large proportion of patients can do well with quarterly injections, and of course, the ALTAIR and ARIES data, looking out to 16 weeks. We have to balance those. And it comes down to individualization with the patients in the trenches where we are. We look at large populations in the studies, but in the trenches, where you have a patient who's coming in and scared to be in your office, scared to be in your waiting room you kinda have to look at that patient's clinical characteristics, and if there's a sign that this is a patient who's dependent on the injections, you gotta try to give them the injections, because of that correlation to injections and vision and the risk of irreversible vision loss, with a recurrence that you saw in your lab study, and we see in some of these cases.

Dr. Singh:
Yeah. I would say my experience in this pandemic has been very interesting and learning how to streamline my practice I think we weren't necessarily the best at doing that. We have really gained a lot of efficiencies. Simple things like moving the imaging closer to where you are you know, skipping imaging when you don't need it. I think we order so much imaging on a knee-jerk basis, and maybe that wasn't the right thing to do for a lot of times. We just did it because, you know, we didn't want to bother with maybe, you know doing the extra investigation before we sent the patient for imaging, rather than get it beforehand. That's changed a lot. And I think you're right about seeing patients now. I mean, the lapse study that we did, both in DME and AMD really showed significant detriment to these some of these patients, and I'm seeing them now. I've seen I think I feel like I've seen sicker patients than ever before, but I feel like I'm spending more time talking with them as you all have tonight to the patients about, you know, making sure it's important for them to come back, and showing the pictures or something a surrogate, something to show them that there is a need to come back and get retreatment over time. So, I think you all made very, very fine points tonight with this discussion. And, so with that, I'll end tonight's discussion. Thank you to my panelists and friends for joining me on your evening, and thank you for all of you for watching. For those who would like to claim CME credit you're gonna get an email with instructions, in order to get the CME credit. There's probably a very simple, easy, question four-question quiz you'll have to answer but other than that, you should be able to get it with much ease. And thank you for joining us tonight. This will be archived on the iVista medical education website, along with a variety of other webinars we've done in the past. So check it out sometime, and you'll find a lot of great information for your practice. Thanks again, good night.

Dr. Eichenbaum:
Thanks.

Dr. Bakri:
Thanks, guys.

Dr. Dhoot:
Thanks.

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