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When “Mild” Matters Most: Closing Clinical Gaps in Early Symptomatic Alzheimer’s Disease

Announcer:
Welcome to CE on ReachMD. This activity, titled *When “Mild” Matters Most: Closing Clinical Gaps in Early Symptomatic AD,* is provided by Medcon International and supported by an educational grant from Eli Lilly and Company.

This replay of a live broadcast discusses practical approaches to closing clinical gaps in early symptomatic Alzheimer’s disease.

Dr. Weisman:
Hi there. I'm Dr. Weisman, and we are here to talk about mild and why it matters, and how we can sort of close these clinical gaps from early detection into treatment with this new wave of anti-amyloid therapies. So I'm Dr. Weisman, and I'm on the right of your screen, and Dr. Cabral is on the left of your screen. We're going to be presenting today, and I'm up first.

Here's our agenda: Welcome and introduction—I think we just did that—and why we sort of care about recognition and referral thresholds, how to get amyloid confirmation and overall think about eligibility, initiation and monitoring, sort of operational questions and problems and solutions to those, and how to coordinate care, shared decision-making, and then we'll end with a Q&A session. So please keep your questions to the end.

These are our learning objectives. It's a passion to take care of these patients, a pleasure to take care of these patients. You really can't do it if you don't know how to adequately assess these patients, work them up, and then keep them safe when you are dosing them. So that's what we're going to talk about all today.

Okay, so I'm going to take it first and talk about early recognition and referral thresholds. Here are my disclosures. Mostly, I do clinical trials, and that's historically what my job has been. Also on some advisory panels and do some speaking. And I'm going to launch into something that should be very familiar to everyone who deals with Alzheimer's disease, which is the notion that Alzheimer's disease is pathologically defined, and it's always been that way since Dr. Alzheimer saw the first case. But now we know that the clumps of stuff that he saw in Auguste Deter's brain are proteins, and these proteins build up in what's called an amyloid cascade, and we see that up here. And the canonical view is that amyloid gets snipped out of a mother protein that's called amyloid precursor protein, and it gets processed and spit out of a cell where it should leave your brain. But if it doesn't, it starts sticking together into these oligomers and protofibrils, which further aggregate and they go into plaque, and that's what Alzheimer saw. And he didn't know it was due to this cascade at the time; he just saw it and described them. And because of many, many experiments, we know that downstream of amyloid comes tau. Tau gets phosphorylated and starts sticking together into these tangles, and the tangles kill the cells. And so that's one way of looking at it. With the nerve cell and the amyloid coming out and seemingly causing tangles, although no one knows exactly how that and why that happens.

Here's another view of the same thing: amyloid builds up, then tau, and then neurodegeneration. Amyloid, tau, neurodegeneration. One can have neurodegeneration without having Alzheimer's disease. People can present to us with memory loss. It could be due to a

different protein. It could be due to Lewy bodies. It could be due to TDP43. It could be due to herpes encephalitis. It could be due to vascular changes. If they do not have amyloid, it is not Alzheimer's disease. So that's a really important point. No amyloid, no Alzheimer's disease.

Okay, so here is a kind of a stylistic thing. I would like to just put this into your brain. Alzheimer's disease is a difficult diagnosis to make, and it's a difficult diagnosis to disclose. And yet, it's so important because you can really kind of take the toxicity out of an entire family relationship by just saying the name. And here's my little cartoon to make you remember it, “Say my name,” right? Heisenberg says, "Say my name. You know it. You know my name." Don't turn around and talk to your medical student or resident and say, "Oh, classic case of Alzheimer's disease." Tell it to the family. Tell them your thoughts, kind but candid. And kind of what I do, I like to rip the Band-Aid off early, first visit. If I think it's Alzheimer's disease, then I say this is myocardial impairment. I think it's due to amyloid. I think this is early Alzheimer's disease. Alzheimer's disease, I think, is due to amyloid in your case.

And then know what, there's a rule-out. Get imaging, brain MRI, look for macroscopic changes that leaves the microscopic world that's affecting their brain, thyroid B12. And then if appropriate for an anti-amyloid therapy, then APOE because we want to get that for risk, and we can get blood-based biomarkers. And as we'll see later—more on this in a second—those are very reliable.

And I try to tell medical students and residents and even other doctors, don't be afraid of the diagnosis. You cannot see the amyloid when they're there, but you see the effects. You see a gradual onset of memory loss. You see a slow progression. When you test them, you give them apple, table, penny. After a moment, they cannot remember it. So you're seeing the effects of the disease before you see the protein.

And it's okay to be wrong. It's okay. I love actually telling people who I thought had amyloid that you do not have amyloid, and therefore you do not have Alzheimer's disease. You have a different protein, or we have to get investigate your sleep and mood a little bit deeper, because you don't have amyloid, and no amyloid, no Alzheimer's disease.

So we're going to talk about a vignette. Here's a 58-year-old woman, Caucasian, university degree. She works in a family business, and her grandfather had Alzheimer's, so she's seen the disease. One-year history of memory loss. That's pretty good. Difficulty remembering names of clients and tasks at her job. Pretty typical. She's 58. She still works. She has anxiety, hypothymia, kind of related to her concern. And she's been evaluated by primary care and some cognitive tests, normal range. So that's very reassuring to her. And a lot of people, because those are normal, they think I'm normal, and that ends it until they get worse. And that's not appropriate. Okay, there's still something wrong here. She has a complaint, and it should be fully addressed, even if she tests well. So she's referred, thankfully, to a memory center for further evaluation.

Past medical history of familial high cholesterol, migraine, thyroiditis. She's got normal thyroid function. She's on a statin. The initial evaluation, her examination is normal. Her Mini-Mental truly is great, but she's 2 out of 3 on a 3-word recall. And the Mini-Mental, because there's such a brief latency with those 3 words, 2 out of 3, it's pretty good, but it may not be normal for her, and that's the question you have to ask yourself. She has no impairment to activities of daily living. Her brain imaging is completely benign. White matter hyperintensities are minimal. Those can be actually associated with amyloid and are not to be taken as vascular dementia. That is not appropriate in this situation. There's no microhemorrhages and no superficial siderosis. Her routine blood work is normal. Her thyroid is normal, and she's APOE3/4. So that already should change your opinion because now we know that she has an APOE4 allele. So your antenna for amyloid should go up. People with APOE4 can't get rid of amyloid very easily. They cannot digest it. They cannot shed it out of their brain, so it's more likely to build up.

Again, MRI recap: It's negative, and you can see the images, and there's—really, if there's any hippocampal atrophy, it's below my sensitivity to see it. Maybe increased ventricle size. So I think this one's right down the plate. I would not have ordered neuropsych evaluation, but it's valuable when there are confounders, and she has mild deficits in learning and verbal memory. I think, because time is brain, it's more important to get, in a case like this with no confounders, get confirmation and then go from there and not wait for neuropsych evaluation, but if it's available and you get them in quick, then that's great. So that's the neuropsych.

She has MCI, okay, and there are contributors to this, and these are confounders. Anxiety is also a neuropsych feature of the disease, but we wouldn't want to attribute this to pseudodementia. I think that would be inappropriate. Depression, same thing. But the likely contributor, the biggest contributor, is likely amyloid, and amyloid causes Alzheimer's disease. So this is very likely Alzheimer's disease, just in the very beginning onset, 1 year into it, and she's still in the MCI range. To the family, this is good news because we really caught

it early. “Thank you so much for coming in.” Build a therapeutic relationship with them right off the bat. “Thank you. We're going to catch this early.”

What next? The only thing that's been not done—MRI done, APOE done, check mark. What's not been done is biomarkers. So we don't have amyloid confirmation, and one could consider blood-based biomarkers in this day and age because they're basically on par with CSF in terms of their sensory specificity. And if your pre-test probability, which is the case here, is very high, and you add a test that is very good because of your Bayesian priors, you're very likely to get the truth.

Okay. Here's a schematic of those blood-based biomarkers, and you kind of see below a certain cutoff, you're very unlikely to have it, and above a certain cutoff, you're very likely to have it. And these indeterminate cases occur, and if it's indeterminate, then in the setting, really, you have a suspicion for amyloid, push through with CSF or PET scan.

This is another slide that just shows amyloid biomarkers in primary care to show that it can be useful in primary care if the primary care doctor takes the ownership of getting the test and then acting on the test. They have to act on it. And maybe the prior, the pre-test probability is not quite as high as in their hands as us who have the privilege of not only expertise but time with a patient. We can spend time with a new patient.

But in summary, for this patient, MCI, and then she gets CSF biomarkers, and her ratio of amyloid is low. So her 42 to 40 ratio is low. Why? Because she's not shedding it out of her brain; it's sticking together. Her total tau is high. That's increased, and that's abnormal. This is very much consistent with positive amyloid biomarkers. She's actually APO3/4, but she's eligible for anti-amyloid therapy.

So the key message: Evaluate these patient symptoms, don't take the age. False reassurance is the kind of the devil here, especially for young people. Subjective interpretations, their interpretation of their disease can be all over the place because insight is variable. Your interpretation of risk and comorbidities can also be a confounder. Blood tests incorporate early help, and I rest the biomarker positivity on blood tests over the past year or so with FDA approval. And then, please, refer if you’re a primary care doctor. You should hopefully, fingers crossed, have a guy, have a gal to make those referrals quickly and make them timely because time is brain.

And now I'm going to turn it over to Dr. Cabral.

Dr. Cabral:
Thanks, Dr. Weisman. That was a fantastic intro and overview. I'm Dr. Dani Cabral. I'm an Alzheimer specialist, neurologist, and psychiatrist, and we've heard how to identify the right person with early symptomatic Alzheimer's disease, get properly referred with a specific case of Maria, worked up well, biomarker confirmed, treatment eligible. Kudos to Maria, 58 years old, went to get evaluated, and her healthcare team took her seriously and moved quickly. So bravo to them.

So I'm going to now shift to the how. So the operational triage framework to determine who's eligible, how do we triage them, and amyloid confirmation, how do we do that that actually stands up and holds up, given this concept of pre-test probability.

So we heard from Dr. Weisman. So to determine who's eligible for anti-amyloid treatments, there's really 3 big areas. So they must have this early symptomatic stage of Alzheimer's disease, which is mild cognitive impairment or mild dementia based on symptoms, and then we must have positive or clinical evaluation. Then we must have the amyloid confirmation, and so that could be done with amyloid PET, with CSF, and also now with blood tests. So we'll talk more about that shortly. And then we need to exclude any other possible non-Alzheimer's reasons for this cognitive change, and any kind of unstable medical illness, other factors that people aren't eligible for these treatments. Those who are on anticoagulants are typically not considered eligible. Then this requires clinical judgment.

Now, the baseline MRI is crucial in determining if someone is at risk of ARIA, and so you can see the list here currently of what we consider to, looking at their brain at baseline, what puts someone at increased risk? So I encourage everyone to memorize this list because it comes up often, and we want to know this when we're looking at that MRI, so more than 4 microhemorrhages or a single macrohemorrhage, any superficial siderosis, vasogenic edema, more than 2 lacunar infarcts, or a larger infarct, and then severe subcortical white matter changes.

Now we know we have these 3 tests now, these 3 approaches to confirm amyloid status, and I'm not going to go into all the mechanics of these, but just to say that there has been a huge practical shift in the last 2 years with the advent of blood biomarkers becoming

available and shifting from emerging to now first-line screen in a lot of clinic workflows, and so that changes how we triage things, absolutely, and it's why we want to spend a good amount of time on this today.

So the name of the game here is pre-test probability, and if you get nothing out of what I'm talking about today, this is the most important thing I would say, and this is a real change for us in the Alzheimer space and the neurology space. This hasn't been on the top of mind, yet when it comes to interpreting amyloid biomarkers, this is crucial. We must base the biomarker result on the clinical picture, the person sitting in front of you, right? So this could be the same test, same 90% sensitivity and specificity, yet completely different result depending on who you're testing. Completely different meaning, right?

So here we have 2 different cases. So we have a 75-year-old person with a typical Alzheimer's amnestic syndrome. They're a little older. They have that short-term recall issue, maybe that verbal fluency issue, and so they have a pre-test probability of amyloid pathology at 85%. And so when they have the positive biomarker test, that's going to be 98% accurate that that's a true positive test. Now, if you have someone who's a 60-year-old with subjective cognitive decline, their starting point before they ever get these biomarkers, what we expect is that their pre-test probability of amyloid pathology is lower. It's at 20%. So say they do have a positive Alzheimer's amyloid biomarker result. So that 60-year-old, there's only a 69% chance that they have a true positive test result, right? So that's 31% chance that that's a false positive, and that's really crucial, to consider that person right in front of you. Okay?

And so that clinical exam, this is where I say no time soon we're going to be worked out of a job by AI because that clinical judgment and exam and intense extensive evaluation is crucial and equally important, or more so, to that biomarker.

So let's shift to what we know about ARIA risk assessment. Now, the APOE status is the single biggest risk modifier for ARIA, and so it's important that we know the status. And specifically, we know that it's the 4/4, the homozygotes, who have the highest risk, and this bore out in the clinical trials and also now in the real world. And so we saw that there was about a 42% of ARIA-E incidence in individuals who are 4/4s. And in the Clarity AD specifically, that's the trial of lecanemab, there was 32.6% chance of ARIA-E if you were an APOE4/4 compared to a noncarrier, there was only 5.4% risk. And so this has led to some countries banning individuals who are 4/4 homozygotes from being able to receive these medications. Now, the US FDA doesn't have that exclusion, and so I'm glad about that. And I think these individuals deserve the conversation and to have that shared decision-making when it comes to knowing their risk and deciding if these are the right treatments for them.

Otherwise, other ARIA risk factors. Importantly, we talked about this, the baseline MRI finding. So if there are markers suggestive of cerebral amyloid angiopathy, and you can see here this list of different kinds of blood and blood products, and the amounts. So we have treatment. We have appropriate use recommendations of which of these determine if someone's not eligible or at notably higher risk, right, and so this all factors into how we're going to present to the individual in front of us their personalized risk assessment, and so we're doing the best we can with the information we have, right? Any kind of prior cerebral macrohemorrhage, a larger hemorrhage, or severe white matter disease, and even moderate to severe are additional exclusions.

So talking about the appropriate use recommendations when it comes to these APOE4/4, the homozygotes. So with lecanemab, the AUR say people who have the 4/4, they're at increased risk for ARIA with lecanemab, and the risk may be also increased with antiplatelet agents. And so what's recommended for those individuals is to have another ARIA surveillance MRI before the 26th infusion, and then the donanemab appropriate use recommendations for the APOE4/4 homozygotes, they strongly recommend that clinicians proceed with caution in this population. They don't say it's an absolute exclusion. And so at the end of the day, the name of the game is always clinical judgment, right? And so I think, once again, we have that option here in the US, and I'm grateful, and I know patients here are grateful to be able to use these medications who are 4/4.

Now, other things to consider for ARIA risk would be—2 other important factors are anticoagulation. So concurrent anticoagulant use is contraindicated in individuals who are on these therapies because of this increased risk of bleeding and risk of ARIA progressing to intracerebral hemorrhage. And we have seen, unfortunately, some fatal hemorrhagic events in individuals who are taking concurrent lecanemab or donanemab with anticoagulants, and the majority of these were in individuals who received TPA because they presented to the emergency department with stroke-like symptoms. And so we'll talk more about that and how to mitigate that risk.

And then finally, the higher the antibody dose, as the dose increases, the ARIA-E incidence increases, so that's not surprising. We're removing more amyloid the higher the dose. So those are all the important things we need to consider in terms of ARIA risk and especially as it relates to APOE4/4 carriers.

All right, now I want to shift to the important specific MRI types of sequences and specific recommendations when using MRI to determine the risk of ARIA at baseline and then to monitor for ARIA as treatment initiates and proceeds. So the American College of Radiology is involved in this, and they have recommended with their appropriate use appropriateness criteria. So we need to include—this is the minimum sequences, right? So in thinking about you have your Marias in your clinic, and you're going to order the MRI. We want T2 FLAIR. That's going to look for the vasogenic edema and white matter abnormalities. We want T2 GRE gradient recalled echo and/or SWI sequence, susceptibility weighted imaging. So this is looking for blood. This is going to detect your microhemorrhages and your superficial siderosis, and then DWI to evaluate for any kind of acute ischemic changes. And then ideally imaging is going to be on a 3T, 3 Tesla, scanner versus a 1.5. So 3T is going to be better. And we're clinicians, if we want to get as much certainty as possible about the ARIA risk, the better quality, the stronger the MRI, the better to detect these things.

Now we're going to bring in these blood-based biomarkers and a workflow of how you might incorporate these in your actual practice. So here we're talking about using p-tau217, which is one that seems to be coming up at this point as the strongest, most accurate, and most workable, and the possible results of this are positive, negative, or intermediate or indeterminate. And so once you get that result, you're going to have to determine is a confirmatory test needed? And an important piece of that is what's your pre-test probability going into it? What did you expect to get? And if there's a discordant result, that is when you absolutely need to get a confirmatory test with either the amyloid PET or the CSF, and then we can move towards treatment planning based on those results.

As well, if it's an atypical kind of clinical picture, the blood test, the result, might just not feel like it fits with what you're expecting, and then it is reasonable to move toward the other confirmatory tests. And of course, these are harder to access, especially in rural locations, they're more expensive, so it's important to think about these things before this workflow is even started.

Now, of course you only want to use validated lab-grade assays with published cutoffs. There's a lot of blood biomarker companies out there and a lot of attempts to make money on this. So you want to know which are the best ones and the most validated and use those. Otherwise, of course, documenting where you got the result in the chart, and that's important for when you're trying to pursue prior authorizations.

All right, so this first column is a 7-step workflow, clinical workflow. I encourage anyone who's not yet really doing this but anti-amyloid curious to get these slides, which you should have access to, and incorporate this into your clinic because having these standardized systems in place and easily accessible, and your staff trained on it, is going to make all of this flow much more smoothly. So this goes through everything we just described, and I won't go through that step-by-step, but you have it right there. But it aligns with what we just said.

And then the right-hand column, we have the appropriate use recommendations documentation checklist, right? Because we want to put it all in the notes so that the payers, insurance companies, aren't going to push back and say you didn't do this, you didn't do that, and so you need to demonstrate all of these factors that we talked about. What makes someone eligible? What is their diagnosis? They need the mild cognitive impairment or mild dementia, their cognitive scores, their amyloid confirmation, their baseline MRI report, including all of that is essential medical necessity. And this even goes to getting the amyloid PET, including all of this is going to help save you from having to spend lots of time arguing with payers.

So if we go back ultimately to Maria, again, good for her for getting in so quickly, and this is really important and you keep in mind her pre-test probability was high, her results aligned with that, and so it fit, and we could move forward quickly with getting her on her treatment because, as Dr. Weisman said, time is brain here.

Dr. Weisman:
Time is brain. Why? Because early is better, and when they're outside that window, unfortunately, that's a different discussion, and that is hard. When people are more moderate, they're no longer appropriate. If they only have subjective memory complaints, and in my judgment they do not have MCI, then that is also not appropriate at this time. So obviously it's going to be early, confirm amyloid pathology, and no major exclusion findings. And I like the way that's put, your exclusion findings. You mentioned white matter change. Some of those are a little bit subjective depending on the radiology read, depending on my interpretation. Yeah, but obviously, if you have 5 or more microhemorrhages, multiple areas of superficial siderosis, it's just not a good fit. The drug is not for everybody.

Dr. Cabral:

Yeah, there's other options. Yeah. Okay. Thank you.

Dr. Weisman:
Okay, I'm going to take it. So thank you for that. And I guess reiterate the take-home point is pre-test probability and know the patient, get a sense of the partner. Maria was 1 year, and everything is in accordance. She's super mild 1 year into it. It really matches what we see. But if there is incongruent inconsistencies, even in the history, you might not be dealing with a very reliable caretaker. There's something wrong, and that patient might not be the best with blood-based biomarkers because you don't have proper clinical context.

Okay, so I love this slide because it shows the binding characteristics of all of the monoclonal antibodies, including the ones that haven't worked. So possibly the reason why solanezumab did not work is because it only binds to the monomers, and that there are so many monomers in the brain, and it's so hard to get a monoclonal antibody into the brain that the monomers might just suck them up, and solanezumab did not work. Gantenerumab is interesting. They're approaching gantenerumab with now a brain shuttle program. It's the same antibody but gets into the brain with more penetrants to overcome the blood-brain barrier, and so it comes down to basic pharmacokinetics and hopefully, fingers crossed, pharmacodynamics and a good effect. Aducanumab, very controversial, 1 positive trial, 1 negative trial, and ultimately abandoned because lecanemab has noncontroversial results that were positive. Lecanemab binds to little clumps of amyloid, and it also binds—it looks like clears away plaque-type amyloid. Donanemab only binds to plaques, and once it binds to a plaque—all these antibodies kind of work the same way. They bind to the plaque, and then they create a situation, opsonization, where the microglia then bind to the FC region in the antibody and then pull out the amyloid, and then a lysosome digests the amyloid, and so the amyloid is reduced based on that mechanism.

And here's what we're looking for. What we're looking at is what the patients are looking at. They're all very mild, but they're looking at progression. It's the landing, and people really fear moderate Alzheimer's disease, actually, more than death itself. They fear loss of control. They fear being a burden on their family, and I hear them when the rubber hits the road, “I would rather die than get like my uncle or my mother or”—if they've seen the disease before. And not everyone has, so there is some education that has to take place that you're mild now, but in the future, because of the progression of this disease, you might not be in the future.

So what we're looking at is this: we're looking to get them up to a milder trajectory, a milder slope, bringing them from a moderately hard slope, if you're going to ski that, into the bunny slope. I want everyone to be on the bunny slope or even just flat. I would love that. That's not what we get. What we see is a 30% reduction in progression that translates into about 5 to 6 months months over a year and a half of time spent in a milder state.

We expect increasing drug-placebo differences over time, and we push the disease up this way, that's not what they're going to really see, they're going to perceive, and that's what they want is more time pushing the disease further in terms of time, staying milder for longer.

And then enduring effect. I mean, we've shown now, and Lilly has been great at this, at showing that if the donanemab achieves treatment-related amyloid clearance and they become completely amyloid cleared, that they continue to have an enduring effect. And then what we don't want is this. And unfortunately, if something bad happens to them, the drug, a rapid progressor, will actually have progression, and then de-escalation conversations have to occur. And the way that I do that is I maintain my advocacy for them by saying, “We can try you off of this drug. We'll make an appointment in 2 months. If there's been a big decrement in terms of slope and it's gone like this, then we can reconsider.” And they know that I still have their back. I'm still in their corner in that way.

Okay. So time to event extended, kind of already mentioned. Time saved already covered.

Okay, and this is the way these drugs work. When PET scans are measured over time, the people on placebo accrue a little bit more amyloid. The people who are treated become negative; they go toward negative. And here's a representative PET scan where someone has gone from positive, they got lecanemab over 18 months, this just happened to be lecanemab, and they went to negative. And this is a colorized PET scan, where no more amyloid is present, so the ligand can't bind to the cortex anymore.

And we see the same thing with donanemab, and it's fairly rapid and then deep. And for this drug, we could consider checking a PET scan at a year. It's about 50-50 whether it's negative, or a year and a half. At that time about two-thirds can go off the drug, and one-third could continue.

Okay, clinically, this is actually from the slide. And again, we have this in our consent because it's so important to be able to talk about the real trial data, so they have that information to make a good decision. Untreated, on average, people will decline. Treated, on average, they still will decline, just at a slower rate. And if we draw a line backwards, it's about 5 to 6 months of mild, below which it gets worse, and maybe they're having more difficulty with something—picking up the grandkids, or making financial decisions, or remembering financial decisions, something like that.

Okay, ARIA. So that's all the good stuff. This is the bad stuff. Amyloid-related imaging abnormality, the feared complication of these drugs. So it's an imaging finding. That's why it's called ARIA, imaging abnormality. We want to keep it an imaging abnormality only. And the way you do that is exactly what Dr. Cabral said, which is do not skip an MRI. And any time they have a whiff of possible symptoms from ARIA, a headache in combination with visual change or walking difficulty that's new, it's okay to just skip a dose, get an MRI, see if they have any ARIA. And if they don't, re-dose and treat them symptomatically. And if they do, then treat them with steroids.

And so what happens here, and the pathogenesis is very important to know, that amyloid builds up in the brain, and then Maria presents to us with memory problems. Amyloid also builds up into blood vessels, and when it's in the blood vessels, and we remove it, then holes form. We don't know why, but the holes form in the blood vessels, and that makes vascular permeability happen. And so the plasma that's supposed to be in the blood vessel leaks out into the brain. Or, if it's a bigger hole, then a piece of blood will actually ooze out into the brain, and that's called ARIA-H. Plasma, edema, brain swelling, ARIA-E. Blood ARIA-H, little bits of cells that come into the brain. And if they come into you with ARIA-H, as demonstrated here by numerous areas of superficial siderosis, not a good candidate. Okay?

And here we see deep white matter and thalamic microhemorrhages. If you see ARIA-H with no ARIA-E, then you know that a big hole must have leaked out plasma. It leaked out blood, so that ARIA-H is there. But if there's no ARIA-E, it's old. Okay, the ARIA-E went away. The edema result that ARIA-H. It can get better, but generally it's more of a MRI would show stability in these patients, and another MRI for the ARIA-E folks will show gradual resolution. Although it can get worse until it gets better, but gradual resolution until it goes away.

And then if they're being treated and you got ARIA-H, it can happen spontaneously. Then have a discussion with them and say that here you had it before, you could get it again, you might be prone to getting it again, but we're okay to re-dose you because your ARIA-E has gone away and ARIA-H is stable if it's present. Okay?

So that's pretty much what I said. ARIA is typically asymptomatic. So the biggest symptom, I tell the patients, is your phone is going to go off because we're going to catch it early. And when symptoms occur, they're usually mild to moderate.

But as Dr. Cabral mentioned, there have been catastrophic cases of ARIA, and you don't want that to happen. You want to do no harm. So be wise with those people with anticoagulation who can't get off it. Very serious discussions about risk versus benefit.

Okay, so ARIA is divided into mild, moderate, severe. And this is a mild case. It's very small, less than 5 cm. This is more moderate, 5 to 10 or greater than 1 location, and this is severe. It's 1 location in this case, but it's greater than 10 cm. ARIA-H, also mild, moderate, severe. And superficial siderosis 1, 2, and 3, mild, moderate, severe. And the FDA guidance for this permits dosing in mild cases of ARIA. I'd encourage you, if you see ARIA-E, you know that's the acute and subacute event because you've done that. That's the vascular permeability. You can develop a microhemorrhage outside the setting of ARIA-E because the blood can consolidate into hemosiderin and be picked up at a later MRI, so you can safely dose with 1 new microhemorrhage, but use judgment.

But with ARIA-E, perhaps, I guess, put it in your brain to get a 1-month MRI and check again. And if it was an artifact, so be it; it will be called an artifact. If it was true, it will probably resolve. Okay. Otherwise, wait for stability for longer. And if ARIA-E again goes away, then you're safe to re-dose. If ARIA-H is stable, then you're safe to re-dose. And same thing with superficial siderosis. Okay.

So the other complication—and the real-world evidence is that we've actually had less ARIA, probably due to proper patient selection we've learned from the trials, but we've actually seen more infusion-related reactions. And so lecanemab, it's 26%; that's from the trial, mostly mild to moderate. You can treat them with 20 mg of prednisone. That's what I do, the morning prior, and it's a flu-like reaction. It's kind of like getting a vaccine. During and right afterwards, people can get joint pain, muscle pain, malaise, a low-grade fever, GI issues, flushing, but not an allergic reaction. Donanemab 8.7, most mild to moderate, but the severity seems, just like clinically speaking, to be a little bit more than that, and they're between the second and fifth infusion. And again, they typically go away over time if they can get through that.

That is not to be confused with ARIA. Here are the incidents of ARIA, and there's a big sway. You can see a big swing from APOE noncarriers for lecanemab about 5%, 1 in 20, to homozygous—and Dr. Cabral mentioned this—1 in 3, they're at increased risk. Okay, and the same thing for donanemab, a swing of 15% versus 40%, and most are asymptomatic, but there are some symptoms, and they have to know that information before they sign up to get the dose.

There's a modified titration now for donanemab that may change these numbers and make them lower by about 10% and what they've done is that they've modified the titration. Instead of a half, a half, a half, and then full dose, people get 1 dose or one-quarter, half, three-quarters, and then full dose. And that seems like it really cuts down on the rate of ARIA. So good for Lily for doing this trial. And so less ARIA than quoted in the phase 3 trial.

Other risk factors. So we mentioned APOE4. These people are very much at risk of the disease, APOE4/4 particularly, because there's a big step up. They're more at risk of the disease. They've seen it in their family. They're also more at risk of the side effects. Many of them are highly risk tolerant, so be permeable to what they want. And when you get informed consent, they should really know their APOE allele so they can make exactly their personal risk assessment themselves. Any hint of cerebral amyloid angiopathy, like 1 microhemorrhage, I sort of think about it like, ah, okay, everyone's allowed 1, but 2 or more, up to 4, increases your risk further. Okay, the dose escalation seems like it's a risk factor, and ARIA occurs early, most commonly in the first 2 to 6 months. So that's when you look at the MRI, and that's also when you should have your antenna out for ARIA events symptomatically. High blood pressure is a minor risk factor.

Okay, so if our patients are mild, how is that defined clinically? Who makes a judgment call? You do. You're the clinician. Call it. Are they mild? Take the totality of the patient. A patient with a language variant could be less than Mini-Mental 22 for lecanemab, less than 20 for donanemab, but they could be very functional. Okay, so take the whole patient into account. Okay?

These are the radiology recommendations for MRI monitoring. If there are any radiologists, please ask a question. But mostly speaking to the clinicians, these are for radiology, like what to do and when. And these recommendations are very important to decrease magnet time because that can be a big burden for the MRI centers.

Okay, this is the MRI surveillance, and luckily now it's in kind of accordance with each other. Lecanemab and donanemab, the same MRIs are done around the same time period, and you can see they're very front loaded because that's when ARIA happens. That's when you want to catch it, and if it's occurring radiographically, stop the dose, wait for it to resolve, talk to the patient, consider then restarting. Okay, and then of course you can drop an MRI in an APOE4/4 patient prior to dose 10, who has a little bit of a headache, fine, get an MRI. You're on safe ground.

Okay, ARIA management algorithmic, most are going to be asymptomatic. Okay? And then radiographically, use clinical judgment about when to get another MRI. If it's mild, I would say a month. If it's more moderate to severe, and it can still be asymptomatic, wait 2, 3—I've even waited 6 months in a severe case of ARIA-E. Again, asymptomatic. If symptomatic, obviously we're going to suspend treatment regardless. Consider treatment. So steroids can work; they're not being used for anti-inflammatories. We're firming up the blood-brain barrier and decreasing the brain swelling that way. And then again, when symptoms fade, if they fade, then consider stability on ARIA-H, resolution of ARIA-E, and then re-dose. Consider re-dosing.

Here's, again, to reiterate, rarely serious and life-threatening events can occur. Intracerebral hemorrhage have occurred in patients treated with this class of medications usually confounded by anticoagulation or thrombolytics. So there's a fear thrombolytics should not be given to people on anti-amyloid therapies. We don't really have the safety information yet, particularly when ARIA is the greatest concern at 6 months. If, on the other hand, somebody's been on anti-amyloid therapy in the past and has stopped, you might be on safer ground after a year-ish. You might be on safer ground. Again, use clinical judgment for thrombolytics. An LVO, on the other hand, may want to just go in because we know what happens if an LVO is permitted to stay in the brain.

Okay, handing it off to you, Dr. Cabral.

Dr. Cabral:
Thanks, Dr. Weisman. So now we know who can get these medications, how to start them and monitor them safely, and monitor for ARIA. So now I'm going to briefly talk about how do you create a safe clinical practice with this, creating systems and workflows, and

have the conversations with the patients and families, and multidisciplinary team. So exciting, but definitely got to put in the work to get this sorted out.

So we already know that before we can fix anything, let's look at all the places that this gets delayed. So even if you have someone coming in, they already have 2 to 3 years probably from symptom onset. So that, again, time is brain. The clock is already ticking, and then we have limited specialist access. Biomarker confirmation can be slowed down for different reasons for getting, especially, the amyloid PET and the CSF testing, and limited reimbursement for the blood test, the costs and the coverage of the drug, in the process of getting this approved. There's infusion infrastructure. Many practices don't have an infusion center in their practice, so that can take time to get that sorted out. MRI scheduling bottlenecks. And then the eligibility window. As the clock is ticking, when the person gets to the moderate dementia stage, they're no longer eligible. And we know that these drugs work better the earlier they're given, right? So patients can encounter multiple barriers before ever getting to start on these medications, even despite everyone's best efforts and intentions.

Going back to that mild matters, like Maria, like good for her. She did it perfectly, and so did her team. And so what are the 5 essential conversations you have to have with the patients and families before starting these therapies, and document and share information with them? So contraindications, of course, the risks, and not just the ones we talked about but also cerebrovascular disease. They may be ineligible, and anticoagulants, things like that. Expected benefits of treatment, making sure they have the appropriate expectations, that this isn't a cure, and they're unlikely to even improve. Though we have some data that there is a subset of people who do at some point. But what we know is it's going to slow the disease in terms of biologically and symptomatically. Risks. Of course, talking more about the risks, especially ARIA, and in an individualized way where patients can understand. Commitment and the burden. There's a lot of moving parts here that are very different for a lot of these patients. They have to get regular infusions, MRIs, follow-up visits. They're going to be getting contacted by lots of different people, and the payers are involved, so they might hear about prior auths and things like that.

And I want to add that I have, for my practice, a travel restriction for the first 6 months. They have to stay near a major medical center in case they have ARIA symptoms that require them to present to the emergency department. It's helpful for families and patients to, I think, have that 6-month idea in mind and not like, “My whole life is going to be restricted by the risk of ARIA.” Like, 6 months is the biggest risk. It can happen after that, of course, but it's less likely. And then the costs associated with this.

So this is a standardized referral for treatment referrals for treatment-ready individuals. So you should have access to these slides. So I encourage you, if you don't already have something like this, to include this as a checklist for did they have the right clinical picture? Do they have the biomarker confirmation? Do they have this high-quality MRI with all of the sequences and don't have excessive ARIA risk? We heard from Dr. Weisman about what that is. What is their genetic risk given their APOE status? And were they counseled on this? Other things that could put them at risk, including anticoagulant use, uncontrolled hypertension.

And then the patient and care partner. I call them the treatment partner in this case because the person is usually quite independent. So patient and treatment partner readiness. This is crucial to have this other person on board because our patients have cognitive impairment and memory loss, right? So they may not remember all of these conversations we're having in counseling, and so having that person knowledgeable and on the team is crucial.

So here's where we have talking about the multidisciplinary aspect of these anti-amyloid treatments. So when we want to have closed-loop handoffs—and there's anti-amyloid boards similar to tumor boards, oncology tumor boards, now where it's determined if a person's eligible and working together with the different stakeholders, and so we have primary care, neurology, radiology, infusion center. Then emergency departments, although rarely used, is so crucial, right? Because that could be the true life or death here if the emergency department isn't trained, and the patient and family. So if the patient and treatment partner understand stroke-like symptoms, we heard about the risks of anticoagulants, TPA. What to do when faced with this in the ED? We need to make sure everyone is on the same page with that.

And then here is some things we need to talk about. Everyone has a seat at the table: the patient, the treatment partner, and the clinician. Benefits, risks, monitoring, burden, and treatment navigation. So I'm moving pretty quickly, but you will have access to these slides. And then, of course, emergency risk counseling. We talked about what can happen in the emergency department, and we want ideally to have urgent, rapid MRI to see if the stroke-like symptoms are indeed a true stroke, or are they ARIA, or is there both? And if there's ARIA present, TPA should not be given, and we should do mechanical thrombectomy.

And then so this is basically what that says. It's a workflow for that. And I know I'm racing through this, but this is a good one to go back to and determine ARIA or no ARIA in the emergency department, and are the symptoms mild, moderate, severe, or is it symptomatic ARIA, and what we do in this case.

What do you think will be the greatest challenge, Dr. Weisman, for the audience?

Dr. Weisman:
I think it's multifactorial, and every clinician has their own struggles with disclosure or hostile headwinds that are coming at them from an institution. It's so individualized. I've heard a lot. I mean, I've had a lot of conversations with people, and it's very different depending on the setting and the context that people are working in. I would say I'm a shoulder to cry on, so if anybody wants to dish, I'm very passionate about this, my email is dcweisman@gmail.com. So please email me, anybody who listens. I mean, you can put it in the chat as well. I mean, I'm totally free. Okay.

Dr. Cabral:
Yep, same for me. All right. Want to wrap it up, Dave?

Dr. Weisman:
Yeah, I think we're over time, so I apologize if I had too many slides, but again, it's an iterative process, so we're not going to take the questions. But anyone has any questions, dcweisman@gmail.com. Thank you.

Dr. Cabral:
Thank you.

Announcer:
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