Transcript Details

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Understanding the Fine Print: The Who, When, And What To Do ARIA in Patients with Alzheimer's Disease

Introduction:
Welcome to CME on ReachMD. This activity and title: Understanding the Fine Print – The Who, When, and What to Do About Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease. This activity is jointly provided by Medical Education Resources (MER) and Efficient LLC, and is supported by an educational grant from Lilly. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Galvin:
Hello, and welcome to Understanding the Fine Print – The Who, When, and What to Do About Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease. This is a very important topic, and it has recently come to the forefront in AD. My name is Dr. James Galvin, and I am excited to take you through this activity series.

The field of Alzheimer's disease is quickly evolving and has recently seen the approvals of its first ever disease-modifying therapies. With these amyloid-beta targeting agents now a reality, the entire way this condition is viewed and managed across specialties is starting to change. In particular, these agents have introduced their own unique adverse effect, amyloid-related imaging abnormalities, which will be the subject of this program.

This activity is part of a series of six distinct activities, each targeting the commonalities and unique aspects of ARIA recognition and management across four specialties – neurology, radiology, emergency medicine, and primary care. In this first activity, we are going to give a brief background of ARIA and introduce it, and how amyloid-targeting DMT impact the field of AD as a whole.

In the later modules, we'll dive deeper into the management of ARIA specific to individual clinical settings based on specialty, and in the final module, we will reconvene to discuss the big picture of, and lingering questions in, ARIA management and how clinicians across specialties can work together to optimally manage these patients.

These are our faculty across all six activities: I'm Dr. James Galvin, Professor of Neurology and Director of the Comprehensive Center for Brain Health at the University of Miami Miller School of Medicine. This first part is led by me and Dr. Gloria Chiang, Associate Professor of Clinical Radiology at Weill Cornell Medical College. We also have Dr. Christopher Carpenter, Professor of Emergency Medicine at the Washington University School of Medicine, and Dr. Charles Vega, Clinical Professor of Family Medicine and Associate Dean at the University of California Irvine School of Medicine. So, I want to take a moment to welcome my esteemed faculty. I'm excited to have you with me today.

Dr. Chiang:
Thanks, Jim. Happy to be here.

Dr. Carpenter:
Thanks, Jim. Really appreciate the opportunity to bring the acute care perspective here.

Dr. Vega:
I'm happy to share the primary care perspective. Thanks for having me along.

Dr. Galvin:
So, this is going to be a great interactive panel. We have members from multiple different specialties and really expect some really lively interactive conversation.

Dr. Vega:
Well, so, this is just a snapshot of epidemiology, and the one solace in terms of me, myself, getting older is that I find that it's very contagious. We're all getting older, and as a society, you know, that we're getting more gray. So, the society as a whole is aging, which is going to yield a lot more cases of Alzheimer's disease. By 2050 that population is expected to double. Unfortunately, when it comes to Alzheimer's disease, we also know it's a real graveyard for a lot of investment, a lot of science, a lot of research that does not yield a lot in terms of disease-modifying therapy. In fact, we've been limited to symptom management but now we have so much more, and that's a very, very exciting time at exactly the time we need it as the population ages.

Dr. Galvin:
Yeah, I think that's very true. You know, from the neurology perspective you know, the great unmet need for our patients is something that goes beyond just simply symptom management, so really excited about some of the breakthroughs that are coming.

Dr. Carpenter:
Yeah. In the emergency department as well, we're seeing increasing volumes of individuals who – with dementia, many of them unrecognized with – they have dementia, but they're not recognized, and this is occurring in a landscape where over the last 40 years, our understanding of the neuropathology of dementia i-is just rapidly expanding.

Dr. Galvin:
Yeah, I think this is going to affect all of us. You know, that's why we have a multidisciplinary panel here because this is something that's going to touch each of our specialties, and I think the way we're going to get through this is to work together. So, this will be a lively conversation so as we move on, you know, I think one of the things that's really, really exciting is the breakthrough with disease-modifying medicines or therapies, or DMTs. We're going to refer to them a lot during this particularly the ones that are now targeting amyloid-beta protein and this has a really significant role in the Alzheimer pathology spectrum so as we move through the stages that we know of the disease from the preclinical – that's the asymptomatic people who are – don't have any cognitive symptoms but have amyloid in their brain – to the stages of mild cognitive impairment, the first recognizable symptomatic stages of disease to the people who then go on to develop Alzheimer's disease at the mild, moderate, and severe stage and as people move through these clinical stages, they're accumulating pathology. They're accumulating amyloid-beta protein and tau pathology in the form of plaques and tangles and so now we have these medicines that are coming approved – so in June of 2021 aducanumab, in January of 2023 lecanemab – and those are both approved for people with mild cognitive impairment due to Alzheimer's disease and people with the mild stages of Alzheimer's disease, and we also have a late-stage investigational drug, donanemab, which is finishing up its phase 3 studies, also targeting the same population. This is really exciting. So, we have approved medications that allow us to address this part of the spectrum, this symptomatic, early Alzheimer's disease spectrum.

Dr. Chiang:
Yeah. So, what have we seen in terms of changes in the amyloid burden with these three agents? So, if you look at the blue figure on the left this is the – these are the results of the phase 3 trial with aducanumab, and you can see there's both a dose and time dependent reduction in beta-amyloid, and so this is from the EMERGE trial where you can see, in the placebo group over the 78 weeks, there was actually a slight increase in amyloid burden on PET, versus if you look at the group that received the high dose of aducanumab, there is actually a 71% decrease in the amyloid burden on PET. The other interesting part of this trial was that they also found a downstream reduction in tau. So, if we believe in the amyloid hypothesis, decreasing the amyloid burden also reduced the tau burden subsequently. If you look to the figure in the middle, these are the phase 2 results from the lecanemab trial, and similarly, you can see the placebo group had essentially no real change in the amyloid burden – it's maybe even a slight increase – versus the lecanemab group. They had a significant decrease in amyloid PETs, such that 81% were actually amyloid negative at 18 months, and if you look at the purple figure, these are the phase 2 results from the donanemab trial, which again, the placebo group didn't have much change in the amyloid burden over the 18 months, but the donanemab group had a significant decline in amyloid burden on PET, and 68% were amyloid negative at 76 weeks. So, essentially, all three of these agents were effective in clearing amyloid from the brain as measured on PET scans.

Dr. Galvin:
Yeah. And then this is really exciting because, you know, this is now three – they're all monoclonal antibodies, but they're attacking slightly different parts of the amyloid pathology and they're all showing similar types of changes on amyloid uptake and what they're doing to PET scan and downstream signals. So, Chuck, you know with – let's dive back in and talk about aducanumab, yeah?

Dr. Vega:
Yeah.

Dr. Galvin:
Not a lot of people are using aducanumab, but I think it's important to use that because it was the first approved, and so it's sort of begins us to have – lets us have the conversation. So, you know, one of the questions that's posed on the slide, you know, is removing

amyloid-beta protein – is that enough?

Dr. Vega:
Yeah. It's – it was very exciting. I agree with Gloria. The – those – the reduction in amyloid protein is really quite remarkable, and it seems that it should certainly follow the patients who do better in terms of their cognitive function and, again, going back to their overall function as well and aducanumab is not without controversy when it comes to efficacy because it originally it failed its futility analysis. Investigators went back, relooked at the data, and found that the high dose actually did achieve a statistically significant improvement in one of their main cognitive outcomes and, therefore, that's what they moved forward with to get the drug approved, and then certainly, I think the – which I would love your opinion on, Jim – is because this is what matters to me as a clinician, is this clinically relevant because there are some important safety signals, which we are going to talk about, and while Alzheimer's disease, you know, we have no cure, it's a desperate situation, patients fear this diagnosis more than cancer.

Dr. Galvin:
What I thought was the most important part of this trial, as much as controversial as it all was, to me, one of the most relevant things when I discuss these treatment options with patients is the ADL Scale. So, this is the Activity of Daily Living Scale, and it's geared for the very mild cases. So, unlike the previous ADL scales, which have a lot of basic ADLs – toileting and things like that, which we see effective in later stages – these questions really focus on the types of things that the person with the mildest forms of Alzheimer's disease face and may be having difficulty with, and it was a 40% difference in the high-dose treated group compared to placebo. So, when I think about clinical meaningfulness, this is what really comes home to me. What do you think as a primary care doctor?

Dr. Vega:
Right. Well, I'm exactly with you because that – that also stood out to me because I think I'm really more of a functionalist than anything else. So, you know, how can you get about your day? Are you having, you know, an easier time with your memory? Are you able to follow complex instructions? Is your executive function holding on? I think those are really, really important, and those are the things that make a difference to the patients, and, you know, why they, you know, will be able to put, I think, the right kind of perspective when balancing the potential benefits of a drug like aducanumab versus its risks.

Dr. Galvin:
So, now let's move on to lecanemab.

Dr. Chiang:
So, these are the results from the phase 3 Clarity study of lecanemab, which actually just came out a few months ago, and this study included older adults with mild cognitive impairment or mild Alzheimer's disease, and the main finding was that there was a 27% slower rate of worsening on the CDR Sum of Boxes at 18 months. So, if you look at the figure, the placebo group had significant decline in cognitive function over the 18 months, versus if you look at the lecanemab group, they had a decline, but it was a slower decline over the 18 months, and what was interesting is that they diverged with time. So, that sort of separation between the groups actually continues through the 18 months so because of that, lecanemab was approved January 6th 2023.

Dr. Galvin:
Great, you know, and one of the really interesting things about the results here is that the findings – the analysis was done in a hierarchical fashion, that is, that the primary outcome – the CDR Sum of Boxes – had to be met before the next analysis was completed in statistical and analytic claim. So, I think that also makes this much more impactful in terms of the power of the potential clinical effect. So, one of the things we'd like to do is kind of think about what is the potential benefit of amyloid-beta reduction. So, this was a paper that was published not that long ago. It's a meta-analysis it's in Alzheimer's and dementia and was really to try to evaluate the clinical benefit of DMTs and so what it did was it took an analysis of 16 randomized trials, so all the trial data that was available a-and this is sort of a update of a previous meta-analysis that was done that did not look at all the trial data that was available – only picked certain points.

For example, the other trial, the ACTIVE study, only looked at the Mini-Mental State Exam and didn't look at other outcomes. So, there were a multiple sensitivity analysis performed for each of the analyses just to demonstrate the effect, a-and the results are really quite consistent, right? For each 0.1 unit decrease in the amyloid-beta PET SUVR, it was associated with a 0.09 change in the CDR Sum of Boxes, a 0.33 change in the ADAS-Cog, and a 0.13 change in the Mini-Mental State Exam. So, the more you're able to remove amyloid, the greater the effect on the clinical outcomes. So, there's likely a causal relationship then between reduction in amyloid-beta protein and a reduction in the functional and cognitive decline.

So, you know, we've spent some time talking about the landscape about the pathology. Let's talk about some new classes, some new considerations, and we're really going to dive now into ARIA. This is going to be the real meat of the conversation that we're going to have going forward.

Dr. Chiang:
So, ARIA, again, it's the main adverse effect that we see with these agents. So, there are two types of ARIA – the ARIA-E, the edematous form, and ARIA-H, the hemorrhagic form. In terms of ARIA-E the aducanumab group reported a 35% rate of ARIA-E compared to 3% in placebo. In lecanemab, it was 13% versus 2% in the placebo, and in donanemab, it was 28% versus 1% in placebo.

In terms of ARIA-H, the aducanumab group reported a 28% rate of ARIA-H versus 9% in placebo, 17% in the lecanemab group compared to 9% in placebo, and 31% the donanemab group versus 7% in placebo.

Dr. Galvin:
So, Gloria, what's that mean? Emphasize for the audience what we're talking about. This is all events, whether they were symptomatic or not, correct?

Dr. Chiang:
That's right because most actually are asymptomatic. So, these were actually all events that were seen on the imaging that was used to monitor these patients.

Dr. Vega:
So, Gloria, I had a question if you don't mind for a second, Jim. I was just kind of impressed with the rate of ARIA-H in the placebo group. So, some of these findings, which I know you're going to cover shortly as to what the, you know, radiographic findings that ARIA-H and ARIA-E, like, how – what they actually mean, but is that something that you would expect just that you'd find that many that many cases in folks who aren't taking active treatment?

Dr. Chiang:
Yeah, I think that was interesting to a lot of people, the fact that you have these sort of ARIA-H types of signs even in the placebo group, and then we're going to go through this later as well, but I think it's important to remember that the imaging findings are not specific to ARIA. So, especially with ARIA-H, that includes microhemorrhages, which-

Dr. Galvin:
Right.

Dr. Chiang:
-we see certainly in Alzheimer's patients but also just with normal aging. So, people who are cognitively normal and you know, getting older, we see development of microhemorrhages, and they can also be seen with people with higher blood pressure and things like that. So I think that's why the placebo group also had this – these reports of ARIA-H.

Dr. Galvin:
Chris, in the acute care setting, you know, we really need to use an MRI to see a lot of these effects. Often when people come in through the acute care setting because MRI takes so much longer outside of a university hospital, the choice may be to do a CAT scan. Is this going to change the way ED physicians may be thinking about ordering imaging for their patients?

Dr. Carpenter:
Jim, I think it's going to be interesting moving forward to see, outside of trial settings, what proportion of these symptomatic patients actually present to acute care settings because you – we assume that 100% of them would, but that's probably not the case. These were detected because it's in a trial setting. So, I think we'd have to see a lot more data, what's the pre-test probability of this in this population what is the number needed to test to identify this pathology, and there's so many other conditions that present with some of these symptoms that are going to be much more common. I think we need to see a lot more data before I can sense the shape and change how emergency medicine is delivered.

Dr. Galvin:
Yeah. I think that, you know, I think you're right. I mean, I think the low amount of symptomatic signs probably will reduce the number of people who necessarily show up in the acute setting, but once the trial – out of a trial setting into the real-world setting, you know, these numbers may change a little bit.

Dr. Chiang:
So, diving more deeply into ARIA, if you look at the image in the middle, this is an example of ARIA-E, which is the edematous form, and you can see the circle delineating this high bright signal within the sulci at the right temporal occipital junction, and basically that's fluid signal that's within the sulca – sulci compatible with the sulcal effusion. If it actually gets into the brain tissue and the brain parenchyma, then it becomes vasogenic edema, but this is an example of ARIA-E. In the image on the right, we can see this is a gradient echo image where you see this dark signal within the sulci, and this is blood products or siderosis within the sulci. So, this is an example of ARIA-H, and then the arrows are pointing to these punctate foci of dark signal, which are microhemorrhages actually in the brain parenchyma and so microhemorrhages and siderosis, these are compatible with ARIA-H in this setting.

Dr. Galvin:
The need to look for these microhemorrhages, is this going to change the way we may be ordering MRIs in practice? Because not all the time are these sequences necessarily ordered, and you don't – you may not get all the views that you would normally get. Especially under emergent circumstances, is – it – are we going to have to start to think about how we write the orders for scans? Is that going to change?

Dr. Chiang:
Yeah, I think that's a great point, Jim, and gradient echo sequences are usually pretty standard in the emergency setting because we need this to look for hemorrhage but I think a key issue is you know, we're not going to see these hemorrhages on CT scans, for example so they could be missed on CT scans. The other thing is that, depending on the field strength of the MRI, lower field strengths may be less sensitive in terms of picking up these tiny microhemorrhages. So, that's something else to keep in mind, especially if patients are going to, you know, outpatient more sort of open MRIs, you may not see these findings if the appropriate sequences were not ordered.

Dr. Galvin:
So, we're going to have to help our radiology colleagues by actually giving them guidance for what we're really looking for so the proper sequences are then ordered.

Dr. Chiang:
Absolutely.

Dr. Galvin:
So, you know, I think one of the interesting that – things is who actually gets ARIA? Who's at risk for it? So, one of the first things we know is that if someone is a carrier of one of the ApoE4 alleles, it does increase their risk, and homozygotes, that is, carrying two of the alleles, has a higher risk than heterozygotes, those carrying one of the alleles, and both of those groups have higher risk than the non-carriers so that seems to be a big driver, and that's pretty consistent across all of the studies. So, we know a lot about who's at most risk – proximity treatment, the higher dose of the drug if you had abnormalities on your MRI either cerebrovascular disease or microhemorrhages, and if you're an older patient. The first point I mentioned was the ApoE alleles, and this is interesting because we actually don't normally test for ApoE in clinical practice so I want to put this to Chuck for a second. I mean, think about all the patients you've seen in the last 10 years. I mean, you and your colleagues – is ApoE something you typically think about ordering?

Dr. Carpenter:
No. It's not ordered, and nor is it covered if we wanted to start order it, and it is, it's also a very fraught test because you're talking about you're looking probably prospectively at somebody's risk for developing cognitive impairment, and that has implications for their entire family and so – and yet you know, there are many carriers of of ApoE who don't go on to develop dementia. So, no, it's not something we would typically test for, but certainly in this population, given this data, I think we should strongly consider it.

Dr. Galvin:
Yeah. I think it's going to, again, I think it's going to change the way we're approaching patients, and maybe for those patients we're considering starting a monoclonal antibody as a DMT-

Dr. Carpenter:
Right.

Dr. Galvin:
-we may have to think about screening them for ApoE even though we normally wouldn't do that under normal circumstances.

Dr. Carpenter:
Absolutely.

Dr. Galvin:
So, when does ARIA occur? As I mentioned in the prior slide, most of the events in the clinical trials occurred in the early phases of the therapies so that the likelihood of ARIA is much more – much greater, higher at the initiation of treatment and then tends to decline over time, and that goes along with some of the recommendations about when to image people as the medicines are being started so this is really going to require some enhanced vigilance so the period of greatest risk for the – at least for the approved DMTs so for aducanumab, it's in the first 8 months of treatment, and for lecanemab, it's in the first 3 and a half months, or about 14 weeks of treatment. For the donanemab trial, which is still investigational at this point, most of the events occurred by 3 months – that is, about week 12. So, we have a good idea – it's early on, and we know about how long we have to do this enhanced vigilance for each of the DMTs that are approved and what we might expect for donanemab, which is not yet approved. So, Chris, tell us about what this may represent clinically.

Dr. Carpenter:
I think it's important to understand that the vast majority of these patients are going to be asymptomatic and that we know that ARIA exists in the trial setting because imaging was part of the trial protocol. However, as these agents are increasingly used, these disease-modifying therapies that we're going to see symptomatic patients present into acute care settings, to the emergency department, to urgent care centers, to acute care visits in the primary care office with increasing frequency, a-and we have to have this range of symptoms on our radar so that we're thinking of ARIA as a potential etiology of the symptoms. The symptoms can range from dir – mild symptoms that are frequently covered – encountered in the ED, like headache confusion, dizziness, or visual disturbances, to more

severe symptoms – gait abnormalities, nausea, vomiting, GI upset, to partial blindness and severe neurological manifestation of seizures.

Dr. Galvin:
So, you know, Chris, in the – in an acute setting, the ED setting, someone walks in, and they have headache and confusion and dizziness. The, you know – there's a whole differential diagnosis that probably is running through your head as an ED physician. This is now something else you have to think about if they are taking these medications. So, medication reconciliation is going to be really, really important for these patients.

Dr. Carpenter:
Yeah, and headaches represent 4.5% of ED visits. Dizziness is another 4% of visits, and we've got potential diagnoses that go along with a different constellation of symptoms, so the – but in this right now, ARIA is certainly not on the radar among those differential diagnoses. So, digging a little deeper on the frequency of these symptoms from the trial data we have thus far – headache occurs in about 47% of those with symptoms, altered mental status, confusion – 15%, the nonspecific dizziness – 11%. I would think that, just looking at this data – this is early data from trials – that we really need some ED-based diagnostic research to understand the specificity of these findings and overall diagnostic accuracy of these sign and – signs and symptoms for ARIA in the ED setting. I think most of this data is probably not from the ED setting, and in the ED, it's a bit of a unique diagnostic environment in that we have a very short period of time with the patient, about 11 interruptions per hour for the average emergency physician, and this is currently new paradigm for us to be thinking about. So, it will be interesting to see the diagnostic research that comes out.

Dr. Galvin:
Yeah, and I really like this discussion because I think it really highlights, you know, it, you know, it takes a village. In this case, it's really going to take a lot of different specialties to diagnose and treat these patients but then also manage them once they're starting treatment. So, it's really going to start to change the way we're practicing in a positive way because I think it's going to require more specialty-to-specialty interactions than we might be doing currently. So you know, we've been chatting amongst ourselves that during the – so far during this presentation, but I want to pick some questions and think about how these things might be important to our panel as well as they – how they might be important to the audience that's listening to this be interesting to what you think about this in terms of your practice.

Chuck, in your setting or in your systems, is anybody on DMTs? Is this a common practice that you're seeing?

Dr. Vega:
No, and we have a strong division of geriatrics here at UCI, but I think that they're hesitant in part due to ARIA and then just the – there are other barriers to using the agents we've talked about, you know, just if, you know, how effective are they over time, and then cost is a big concern as well. I do think that the sentiment for primary care in general is let's kind of wait and see. They heard about the controversy with aducanumab. I think lecanemab's data is much stronger, but I would try to really balance that. We are talking about imaging abnormalities that that – so, it's not, I think it, you know, may be a little bit less of brain hemorrhage, which sounds like, oh gosh, we really want to stay away from something like that, and imaging abnormalities, three-quarters of which are – or so are asymptomatic, and we – and then where – what are we treating here? We're treating, you know, Alzheimer's disease, which is certainly one of the most devastating conditions for both the patient and their supporters. So, therefore, I think we need to have some better perspective and get some comfort, and that's why programs like this are really important to talk through some of these issues, and then we can translate that into to good patient advice where they themselves, along with their families, can weigh the benefits and risks.

Dr. Galvin:
Yeah. So, Gloria, in your institution and in your setting, either you or your colleagues, have you encountered patients with ARIA coming in where you're seeing their scans?

Dr. Chiang:
I mean, I would say that maybe we've seen a few so, you know, like many academic centers around the country, we were all gearing up once aducanumab was approved. We had numerous meetings amongst, you know, hospital leadership in terms of how we were going to move forward with this and setting up all the imaging protocols and you know, the resources for lumbar punctures and PET scans and whatnot, and I think once the controversy sort of happened our institution actually bowed out of giving it routinely. So, when we see it, it's mainly from more kind of community type neurologists who are giving it, so but I think with lecanemab there's a plan to move forward so I think lecanemab will be more widely prescribed amongst academic centers.

Dr. Galvin:
Right. Great. And Chris, is this on – is it a topic of conversation yet amongst emergency medicine providers? Or is this something they need to start to become more aware of?

Dr. Carpenter:
No, this is not on emergency medicine's radar at all. We just updated the American College of Emergency Physicians clinical policy on headache diagnosis and management, and this was not, at that time, something that we had been discussing or thinking about. We've

had some controversial discussions at the Alzheimer's Disease Research Center at my institution about some of the controversy surrounding the early trials, but that hasn't really trickled down to the emergency department yet to start thinking about looking for some of these ARIAs among patients coming in with the appropriate symptoms and on these medications.

Dr. Galvin:
Okay. Great. So, what's really important now is that this is a multipart activity, and, you know, we really want you to participate in these activities to learn much more about ARIA in your specific specialty so from this background and introduction, you know, we have activities in neurology, radiology, emergency medicine, and primary care. So, we're really looking forward to having more conversations with you and continuing our discussion the next round of activities.

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