Transcript Details

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

Announcer:
Welcome to CME on ReachMD. This activity entitled, Understanding the Fine Print: The Who, When, and What to do About Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease, Closing Module. This activity is jointly provided by Medical Education Resources, MER, and Efficient, LLC, and is supported by an educational grant from Lilly.

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Dr. Galvin:
Hello, my name is Dr. James Galvin and welcome to the concluding module of 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 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 part one, our panel of diverse specialists gave a background of the key features and implications of ARIA that are relevant to clinicians across all these specialties. In the middle modules, we split up by specialty to dive deeper into the management of ARIA, specific to individual clinical settings. In this module, we'll focus on the big picture of and lingering questions in ARIA management, and how clinicians across specialties can work together to optimally manage these patients.

I'd like to welcome back Dr. Gloria Chiang, Associate Professor of Clinical Radiology at Weill Cornell Medical College, 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. Well, welcome back, everybody. Good to see you all again.

Dr. Chiang:
Hi, everyone. Nice to see you again. Thanks for having me.

Dr. Carpenter:
Hi everyone. Glad to continue this conversation.

Dr. Vega:
Hey, colleagues, great to see you again. And let's get started.

Dr. Galvin:
Now, just to quickly summarize, one of the - some of the things we've covered so far, this is really going to be a team approach. Clinicians across many specialties are going to be able to work together to try to, one, identify ARIA in patients, and then implement the appropriate management and referral strategies. We went over the background of ARIA, the first ever DMT for Alzheimer's have become approved. The main side effects that we've talked for ARIA, the amyloid-related imaging abnormalities, there's two flavors to

this ARIA-E which is the edematous form, and ARIA-H, the hemorrhagic form. It's the most common adverse event in the amyloid-targeting DMTs. Now, most of these cases are in fact asymptomatic. About 74% of people are asymptomatic, and it's really only found through imaging. Of those people that are symptomatic, there's a range of symptoms from mild, which include things like headache, confusion, dizziness, visual disturbances, through the moderate where they start having abnormalities in gait, some GI symptoms, nausea, and vomiting, to the more severe problems where they can have partial blindness and/or seizures. And we went through the impact of ARIA on the DMTs, when the stop therapy. And, you know, there's lots of different recommendations. And I think the most important discussion we had was, you know, not everybody agrees with everything, and that's okay. You know, lively debate is welcome in medicine. We've had some lively debate during our activities.

And so the idea is when you see people with mild symptoms, would you suspend dosing or continue dosing? I think there's some disagreement amongst even the experts as to what's the best way to help manage the patient. The most important thing I think we talked about was to use your clinical judgment. You know your patient well. You're there observing the patient and the symptoms, you've met with the radiologist and talked about the severity on imaging. You have to make the best judgment you can use all the information available to you at that moment.

In terms of when to discontinue, you know, there are clinical prompts, if you have more than two episodes of ARIA, if the symptoms are severe, or if there's any medical condition that requires anticoagulation. I mean, these came out of the aducanumab study, and there are things that we'll be looking at very carefully when people are on lecanemab, and if donanemab gets approved. And then we went over treating ARIA. You know, we went through all the important findings. I think we covered a lot of the major points in the prior activities.

For our group, though, I want to pose this question, you know, how would you counsel patients about the risk of ARIA before prescribing a DMT? Or if you're a writer like Gloria, who may not be prescribing a DMT, if someone's looking to you for advice, what did, you know - what advice would you give people or other prescribers about this? Chuck, why don't you start off? What do – patients –

Dr. Vega:
Yeah, I'm probably seeing the folks most commonly with early cognitive impairment and we're working with a reporter, you know, usually one of their supporters is there telling us about it. And so we are going to talk about disease-modifying therapy. This is certainly something that's in the public consciousness, the idea that there is disease-modifying therapy, a lot of folks understand what that means that maybe not a cure, but something that can significantly improve the disease course for Alzheimer's disease. Heretofore, we never had this. Very exciting. But I think we have to talk about the possibility of ARIA. So I would discuss it with everybody who's interested. And I have had this conversation with several patients and supporters. And it is important to just put things in context that there is a risk of ARIA. Most patients aren't going to have ARIA from the clinical studies. We know that particularly with lecanemab, it does seem to have a lower overall rate of ARIA. And when you have these imaging abnormalities, it's unlikely that you're going to have symptoms.

But I will say that when patients hear about the possibility of brain hemorrhage, they generally will be very nervous, and justifiably so. It's a very scary proposition. So, you know, I think it's important to make the distinction for patients between an imaging abnormality and the way we often think of an acute brain bleed, where there's, you know, a fairly high mortality rate associated with, you know, say, a ruptured intracranial aneurysm in the field. And so I think making that distinction is important.

And I think very importantly, with my patients, it's also getting the buy-in. We have discussed during these activities, the regular schedule of MRIs whether the patient's having symptoms or no. And so I want to make sure that the patient and their supporters are ready for that. And they have to buy into that before initiating the disease-modifying therapy, because if they have tons of barriers around transportation and cost, and, you know, if they don't want to - they just don't want to go through that imaging, then it's going to be harder to recommend. And certainly, I think better to have that discussion upfront, versus trying to have it a month or two into treatment with a DMT.

Dr. Galvin:
Yeah. Gloria, from radiology perspective, you know, if a patient approaches you and ask these questions, or a provider approaches, you know, how would you discuss ARIA to those individuals?

Dr. Chiang:
Yeah, you know, we actually had a very lively discussion, because I remember the lecanemab results came out right when I was at a big radiology meeting, and a bunch of us were sort of talking about, you know, how we were going to move forward with this. You know, what I tell people is, again, you know, brain hemorrhage sounds scary. But again, we see these findings of microhemorrhages and superficial siderosis in asymptomatic people commonly, in older asymptomatic people who are here for other reasons. And so, you know, as Chuck mentioned, it's different than the type of, you know, hematoma you might see with an aneurysm rupture, or trauma or

something like that.

So, the other piece of it is, you know, if you look at the literature, in most cases, once you discontinue the drug, the swelling actually goes away, and the hemorrhage stabilizes. So at least from what we know, it doesn't seem like it causes significant morbidity in most of these patients where we're seeing these imaging findings.

And the other point, I - you know, I'm curious to hear what your thoughts are, is, you know, as everyone points out, you know, if we think about chemotherapy, for example, the side effects from chemotherapy are certainly significant, and probably even more significant than ARIA, but obviously, people take the risk because of the hope that it's effective treatment. So, Jim and Chuck, I'm curious to know what your thoughts were on that?

Dr. Vega:
Gloria, I think it's a really an interesting analogy when we think about treatment for cancer because how often do we hear - and this is our own institutions promoting their treatment model for cancer – 'we're going to go after your cancer, we're going to fight every, you know, last minute for your cancer, you know, we're going get aggressive with it.' And sometimes that is absolutely not the best, you know, course of action, because you have, you know, tumors that are inoperable in patients who are, you know, really high risk for significant side effects, morbidity, and mortality. And we don't think of that. I think as a health system, and even as a broader culture, we don't think of Alzheimer's disease the same way. And this could be that these agents could change that thinking. It's just not there right now. And so. I do think that the fear, you know – and we talked about - I've talked about hemorrhage, but edema is, you know, also something that can be pretty scary too, oh, your brain swells. You know, that's the lay interpretation, also pretty scary stuff. And so I think we have to find that balance, as Jim said, in - for each individual patient in terms of that shared decision-making.

Dr. Galvin:
And last, Chris, I want to make sure you're included in this - is - in again, in the acute setting, you know, what can you and your colleagues - what kind of conversations might you have with patients about this?

Dr. Carpenter:
Well, I don't think in emergency medicine, we'll be in the business of prescribing these medications. I do think we will be in a situation of seeing symptomatic patients where ARIA is identified with imaging. And then conversations will need to ensue about the - with patients and their care partners about the continuation of these therapies. And in a way that uses shared decision-making and reflects the patient's values and priorities in a language that is appropriate for their health literacy. And those are things that are going to need to be developed as we move forward. And certainly in conjunction with the prescribing neurologist or primary care physician, so that we can communicate and make sure that all parties are in the loop. I think that's the scenario we're going to encounter in emergency medicine.

Dr. Galvin:
Right. Right. And that brings us one of - back to one of the first slides we showed during this activity is really going to take, you know, a cross-disciplinary approach to address this going forward.

Dr. Vega:
Chris, I'm wondering if your concerned at just how congested the emergency department can be, particularly with, you know, older adults with chronic conditions, if there's going to be a significant uptick in folks bringing in, you know, their father, their neighbor, or patients coming in themselves, because they have a tension headache. They tripped and fell. And now they're worried because they're on a disease-modifying therapy, they're worried about ARIA and their effects. Is that a concern for you? Because we know how busy it can be? And, you know, how efficiency is critical for good emergency care.

Dr. Carpenter:
Yeah, I think the COVID-19 pandemic has shown us how frail our healthcare system is. Emergency medicine was right at the cutting edge of that challenge. That certainly is a good possibility, and probably will occur. I think that's why it's going to be important for every emergency department to become an older adult-friendly department so that we can promptly recognize these clinical scenarios and deal with them appropriately.

Dr. Galvin:
I think in this case, we're really going to have to get the patient involved much more - much greater in the beginning so they truly understand to the best of their ability, and that their family understands, you know, what are some of the attendant risks? And what's the difference between a symptomatic side effect versus an imaging abnormality that we would only detect because we're doing MRIs? And how to reconcile those differences. Right? Most people think about an adverse event as something that the patient will complain about. Right? That they're feeling something, that they see something. In many cases, this is asymptomatic, and we would never know it even happened if we weren't doing MRIs so frequently. I don't know. Gloria, what do you think about that? I mean, the - right now, with the

treatment recommendations, there's this schedule of doing MRI, we're going to pick up things that we might not ever have known were happening.

Dr. Chiang:
Yeah, I think that's a really good point. And I think the plan is still that patients on this drug will get essentially five MRIs within that first year to pick up the ARIA, especially early on after initiation of this drug, which it involves very close monitoring of patients, but it's also cumbersome for patients. So you can imagine for the patient's family, to keep bringing them into these imaging facilities. And a lot of, you know, patients may be claustrophobic and so we're dealing with those types of issues with all these MRIs. And resources, again, in terms of, you know, allocating these imaging slots to this population. So there's a lot of a lot of issues, I think, to think about there.

Dr. Vega:
There's another side that's kind of interesting to think about, though, because when I talked to patients about ARIA, and then I mention, but we are - you're going to have a regular series of MRIs to just screen and ensure that the treatment is, you know, being tolerated safely. They actually - so you're absolutely right, it's a burden, but they also feel very reassured. I've seen they visibly kind of relax, like, oh, and I think, Jim, comes back that trust factor like, 'oh, well, you'll be watching over this process? You know, okay, I feel a lot better about it now.' So there's a bit of a yin and a yang here. And I see the potential barriers, but certainly I see why it's recommended. And it could be a great reassurance to get patients and supporters on board as well.

Dr. Galvin:
Right. And I guess a follow-up question is, you know, thinking about each of your individual scenarios, I mean, is there the capacity to do this? Right? So, you know, if mild stage MC - mild MCI and mild AD, you know, compose of 3 million or so people, and they're being treated, and they're going to get five MRIs, you know, in a 12-month period. Right? You know, can radiology handle that?

Dr. Chiang:
You know, we've certainly talked about it in our institution, but you know, I think as everyone knows, especially if you're away from sort of large cities with multiple centers, it's very difficult to even get one MRI. You know, there's delays and whatnot. And so I think a lot of practices will be struggling with this volume and getting patients in for these multiple MRIs.

Dr. Galvin:
Right. And Chuck, is primary care ready?

Dr. Vega:
Well, I was just going to refer all my patients to you, Jim.

Dr. Galvin:
I'm not ready.

Dr. Vega:
We know how great you are. I'll tell all my colleagues. So, no, probably, yes. No, maybe so. I think we are - and I think one thing that Chris brought up a couple times, is this is a good opportunity to really think about other risk factors that could go into bleeding. I know with lecanemab, they had in the clinical trial, patients were taking antiplatelet agents, and there didn't seem to be as, you know, I'm kind of surprised there wasn't an increased risk of hemorrhage in those folks. Now people taking anticoagulants were excluded. So that's a group we want to stay away from. But there's other drugs, you know, NSAIDs are frequently used, even some supplements can also promote bleeding. So we really want to stay on top of these things. And I think the primary care office is a really good place to do that. But we just have to make that clear. And that's why again, programs like this are really important to raise awareness so we're thinking about those issues, and then can take the burden off because we can help hopefully reduce the number of cases of ARIA, particularly symptomatic ARIA, or ARIA that might have a bad outcome, because we're following the protocols, we're doing the things to, you know, prevent the severe cases in the first place. And for those cases that develop more symptoms, or significant radiographic signs, we're taking them off the drug.

Dr. Galvin:
All right. Right. And we touched upon this a little bit in our conversations, but what additional patient education might we need to provide? You know, what else do we have to have for the patient? Is it print literature? Is it opportunities to talk to people? Patient representatives available in acute settings? I mean, what are some of the other things we need to do?

Dr. Vega:
We can probably feel a little bit reassured that, you know, since most cases are asymptomatic, you could say, 'Hey, your last MRI showed two microhemorrhages, how you're feeling?' And people will be surprised, 'Wow, I didn't know that. And so I'm still okay, you

know, I didn't have the worst headache of my life. I, you know, everything else is - I'm functioning completely normally.' So I think we can feel reassured for the majority of case of ARIA, we just have to be very mindful of the ones that development, again, more severe symptoms, more significant MRI findings.

Dr. Galvin:
Chris?

Dr. Carpenter:
The Geriatric Emergency Applied Research Network just published a scoping review of communication with persons living with dementia and their family during episodes of emergency care. And we were surprised to find that the real paucity of literature in any scenario, or how to best communicate with these folks. And given that knowledge, I think that we really have to think carefully about how you communicate the findings, the radiologic findings, to these patients, and it's probably not just going to be with the patient, there's going to be care partners involved as well. And I think that our GEAR Network has shown the path forward for doing that.

Dr. Galvin:
So we're fortunate, we're sitting around here and we're having this great conversation and we represent multiple specialties. But, you know, what - if we didn't have this opportunity where we were all sitting around and talking, what do you need from other specialties really to be successful in ARIA identification and management? You know, so how can the radiologist best communicate? What can the - what does the PCP need to know? What does the neurologist need to be able to tell the PCP back? How does the neurologist communicate with the radiologist? You know, where does emergency medicine fit into all of this? Chris?

Dr. Carpenter:
Well, I think what emergency medicine needs to do is when we are ordering these studies for patients with a specific concern, make sure that our order contains that concern so radiologists know what we're thinking, and that this patient is on a disease-modifying therapy that might put the patient at risk. And I think, concurrently, when radiology sees something of concern, looping that back to us that - to put it on our radar that we may not have been thinking about ARIA to begin with.

Dr. Chiang:
Yeah, I think those are great points, Chris. And I think really, for radiologists, we just need the history that the patients on one of these agents. You know, you'd be surprised at how limited our histories often are. You know, because, for example, if I see a patient from the ED who has, you know, altered mental status, and I see two microhemorrhages, I don't really think anything of it. But if it's a patient who's on one of these agents, and I see two microhemorrhages, I'll call the neurologist, for example, or the ED physician, the treating physician. And obviously, it will lead to more discussions in that realm. So absolutely we need to have that history that the patient is actually on one of these drugs.

Dr. Galvin:
Yeah, no, I agree with you. And, Chuck, what about from the PCP perspective?

Dr. Vega:
Actually, if you don't mind, I'd like to turn the question around to you a little bit. I thought there was a mention of algorithms that were presented during the activities that showed, you know, what to do in case of ARIA. But you get a lot of referrals from primary care. Do you think primary care can manage ARIA independently? Or should they really have at least someone on their wing, a neurologist, to assist with the proceeding?

Dr. Galvin:
Well, I think - initially, I think it's going to really require a team approach. And I think neurologists are probably going to take the lead in probably prescribing and managing patients, both with DMTs, and then managing the consequences if they have ARIA. But as you know, there are not enough neurologists to really take care of all the patients, and neurologists tend to be clustered in big metropolitan areas. So if you're in Boston, you can throw a rock and hit a neurologist. But if you're in Montana, it might be several hours drive, you know, to see a neurologist. So I think each PCP is going to have to sort of build their referral network like they do for any other condition and figure out, you know, who's the person that they're going to rely on? You know, and I think this is where potential for telemedicine really comes into play. Stroke care has really changed because an underserved area can have a neurologist manage an acute stroke, right, through telemedicine, and the patient has good outcomes. I think we have to come up with new ways of communicating, and this may just open up new doors for, you know, how we deliver care.

Dr. Vega:
I think one thing that primary care should be very invested in from the get-go is helping to ensure patients are going through that screening protocol and getting there on time. We tend to see patients more frequently than the specialists do. And so therefore, I think

just being aware of the schedule, having it in the record, making sure patients are checking off those MRIs as they go through, especially that first year, is critical.

Dr. Galvin:
So you know, most of the available recommendations we have were based on experience with aducanumab. So it'd be really interesting to see as we get more and more data from lecanemab an donanemab clinical trials, how that might change your view on how ARIA should be approached, what you know of the drugs currently from available studies. So lecanemab is phase 2 and phase 3 study, and donanemab is phase 2 study, still waiting to get the readout of the phase 3 study. Does that that change what we know about ARIA? Does it change your approach in any way? Chuck?

Dr. Vega:
Well, you know, obviously, there's no head-to-head trial comparing these agents which would be the best way to determine if there is a true difference in the rate of ARIA. But just look at the numbers comparing the major trial with lecanemab versus aducanumab, lecanemab is lower, so it suggests to me that these agents, while they probably all have some risk of ARIA associated with them, that that risk can be different from agent to agent and so therefore, we need to follow the literature as more studies come in.

Dr. Chiang:
Yeah, I think Chuck had a great point. You know, at least if you look at the literature, it seems like the rate of ARIA is lower with lecanemab. And so you know moving forward it also seems like lecanemab will be more widely prescribed than aducanumab, in which case, you know, we'll have more real-world data to sort of assess if our monitoring is perhaps too much. You know, do patients actually need five MRIs? Or can we space it out more to, say, three MRIs in the first year? I think that remains to be seen.

Dr. Carpenter:
For the care setting at this stage, I don't think it's going to change our recommendations. Although I think it's going to be important for emergency medicine to understand the differences in the rates of ARIA for the three different choices, and I don't think they're really aware, they just tend to lump them together. From a general standpoint, to Chuck's point, I think it's going to be really interesting to solicit some network meta-analyses that compare each of these agents until we have the actual head-to head-trials.

Dr. Galvin:
I know I'm interested in seeing, you know, what comes of the donanemab trials. And I'm also interested in seeing as real-world data and open-label extension data becomes available, I think it will be critically important to see even longer-term treatment and with larger number of individuals, because, you know, clinical trial populations tend to be very homogeneous, because of inclusion-exclusion criteria.

And Gloria, now there's some interesting data that suggests the extent of amyloid removal may be the most important thing to give you a sense of whether there's a clinical response. What do you think? Or what are you looking forward to in terms of the radiology literature regarding this?

Dr. Chiang:
Yeah, I think from my standpoint, I'm really interested, and I think many groups are looking into this, but more about the mechanisms of what's going on. So yes, we're clearing amyloid. In the aducanumab trial, they did actually have a subgroup that had tau imaging. And it was really interesting to see that clearing amyloid actually decreased tau as well. But beyond tau, there are so many other markers that we can look at. We can look at microglial inflammation, there are plasma biomarkers we can look at, there's CSF markers. So I think there's a lot of interest as to more what are these underlying pathologic mechanisms that these DMTs are actually doing? And how does it relate to ARIA? And are people more prone to ARIA because of some of these underlying pathophysiologic mechanisms?

Dr. Galvin:
Yeah, I'm just really excited. I think, you know, there's so much we don't know. But there's so many studies going on that I think our understanding is really just going to - we're going to be 5 years from now, it's going to be, you know, very different from where we are looking at the picture now.

Well, this has been just an amazing, interactive conversation. I hope the viewers have really enjoyed it. I know I enjoyed it. And I want to thank all of you for participating in the discussion and sharing your knowledge and your experience and your candor thoughts about some of these interesting questions that we were able to pose. Gloria, Chuck, Chris, thank you so much for your participation. And I'm really looking forward to seeing you in the future and having these discussions when we have more therapies and more data to share.

Dr. Vega:
Alright, thank you.

Dr. Carpenter:
Thanks.

Dr. Chiang:
Thank you.

Announcer:
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