## 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 – Radiology Module

**Announcer Introduction:**

Welcome to CME on ReachMD. This activity entitled, Understanding the Fine Print: The Who, When and What to Do about ARIA in Patients with Alzheimer's Disease, Radiology Module. 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. My name is Dr. James Galvin and welcome to the Radiology 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 part of a series of 6 distinct activities each targeting the commonalities and unique aspects of ARIA recognition and management across 4 specialties, neurology, radiology, emergency medicine, and primary care. In part 1, our panel of diverse specialists gave a background of the key features and implications of ARIA that are relevant to clinicians across all of these specialties.

In this module, we'll dive deeper into the critical role of radiologists in the monitoring for, identify, and staging ARIA. To help drive this discussion, I'd like to welcome our representative radiologist, Dr. Gloria Chiang, Associate Professor of Clinical Radiology at the Weill Cornell Medical College, as well as neurologist, Dr. John Toledo, Assistant Professor in Neurology at the Nance National Alzheimer's Center at Houston Methodist. I'm very excited to have you both here with me today.

**Dr. Chiang:**

Hi Jim, how's it going? Thanks for me.

**Dr. Galvin:**

Okay. And – and John, good to see you again.

**Dr. Toledo:**

Thank you. Good to see you. Very excited to be here sharing this data.

**Dr. Galvin:**

Alright. So, Gloria, tell us a little bit about some of the side effects that can occur with the amyloid disease-modifying therapies. How common is ARIA?

**Dr. Chiang:**

So, in – in terms of side effects of these beta amyloid disease-modifying therapies, the main side effect is really ARIA. So, for aducanumab the rate of ARIA-E, which is the edematous form, is 35% compared to 3% in the placebo group. For ARIA-H, it's 28% in

the aducanumab group versus 9% in the placebo group. In the lecanemab group they had a lower rate of ARIA of 13% in ARIA-E group compared to 2% in the placebo group, 17% of ARIA-H compared to 9% in the placebo group. In the donanemab trial there's an estimated rate of about 28% for ARIA-E compared to 1% in the placebo group, 31% for ARIA-H compared to 7% in the placebo group.

**Dr. Galvin:**

So, we're going to talk a lot about ARIA over the next few slides, and I think it's worthwhile just going over that there were 2 different categories of ARIA. First is the ARIA-E, which is the edematous form and so you can see under the slide here that we have this parenchymal vasogenic edema that sort of tracks across the white matter and you can see some effusion as well. The other form is ARIA-Hand there are 2 types that which of what we are looking, the first are microhemorrhages, so these are small, they're less than 1 cm, they're hypointense, and they really represent hemosiderin deposition in the parenchyma. The other type of ARIA-H that we can see is something called superficial siderosis and this really represents a linear hypointense hemosiderin deposition that we see in the leptomeningeal or subpial space.

**Dr. Chiang:**

So, when starting the patient on one of these disease-modifying therapies, it's important to get a baseline MRI. So, as we've shown you a lot of these images of ARIA images that show edema and hemorrhage, it's important to know whether or not the patient already has this as baseline, or if this some – this is something that they developed while on therapy. So, in terms of recommended parameters there were trials that used, for example, a 1.5 Tesla MRI scanner to assess for ARIA. Nowadays it's recommended to use 3.0 Tesla scanner mainly because of the higher sensitivity for microhemorrhages, and to use a slice thickness that's less than or equal to 5 mm. In terms of things to report obviously preexisting microhemorrhages if the patient has them even before therapy is important to note. Whether or not the patient already has superficial siderosis and any other incidental or acute findings, especially acute or chronic infarctions, are important to note.

**Dr. Galvin:**

So, John, let me turn to you here and what are some of the things we have to think about as we begin the initiation of an anti-amyloid therapy?

**Dr. Toledo:**

Based on the protocol for the different proofs tracks we have some timelines when we need to do repeat imaging, for example, for aducanumab, the MRI is done prior to the $5^{th}$, $7^{th}$, $9^{th}$, and $12^{th}$ infusion, and in case of lecanemab it's done before the $5^{th}$, $7^{th}$, and $14^{th}$. And one thing to remember is that the protocols defer in terms of how frequently the infusion is administered, so, when you look at aducanumab, you will see that treatment is given every month, whereas in the lecanemab the infusion is given every 2 weeks.

**Dr. Galvin:**

Right. And – and – and John, I guess the other thing to mention is that we also do an MRI if symptoms suggestive of ARIA occur. So, not just the standard schedule for dosing, but there's also the opportunity that the clinician should image people if symptoms appear.

So, what are some of the clinical correlates we should be looking for in case ARIA is appearing?

**Dr. Toledo:**

Yeah, so, and there are, like several symptoms. Most of them are not localizing, but the most common ones that patients on this treatment experience are headache, confusion, altered mental status, and these can go to most of your symptoms with encephalopathy. Other symptoms that we can see are the dizziness and vertigo, nausea and vomiting, fatigue, gait disturbances, and also vision impairment because there is certain predominant or posterior areas. A less common is like, the presence of atypical changes in the EEG and seizures.

One thing to remember is that, in general, most of the ARIA cases are asymptomatic where approximately 20 to 22% of patients will have symptomatic ARIA-E, and rate of symptoms in patients with ARIA-H is even lower, it's less than 10%. But these are the ones that we need to monitor. The difference in terms of headache prevalence in a clinical trial between patients on placebo and patients who were on the treatment was only like 3 to 6%. So, it might be the case that some of these headaches are experienced normally by patients and are not related, but always the correct approach is to make sure that there are no ARIA that we can find in these additional MRIs that we may order during follow-up.

**Dr. Galvin:**

Yeah. And I think this is a good case where communication between specialties is going to be really important. So, given how important

communication would be, Gloria, what kind of things as a radiologist might you need or want to hear about as you're thinking about these scans?

**Dr. Chiang:**

Yeah. I agree. Communication is definitely going to be important and, you know, sometimes patients come from outside of our medical system, so we don't have their medical records. So certainly, very important for the referring physician to give us the history that the patient is actually on one of these therapies and what their suspicion is for ARIA, because as we mentioned, a lot of these findings in terms of edema and microhemorrhages, they're not specific to ARIA, and so we really need to be tipped off with a history to look for these findings.

**Dr. Galvin:**

With that in mind, when we look at these pictures and when you're looking at these images, you know, what are the grades of severity? How do we know what constitutes just a little bit of ARIA-E versus a lot of ARIA-E?

**Dr. Chiang:**

You know, so there – there is a grading scheme that's been devised in terms of assessing how severe the ARIA is and this is sort of how it's laid out. So, if you look at the first image, this is a T2/FLAIR image. You can see the circles around this area T2 hyperintensity and the left superior frontal gyrus, and also involving the subcortical white matter. Because it's one location only and because it's small, it's less than 5 cm, this would be classified as mild ARIA-E. If you look at the middle image, you can see the T2 hyperintensity, or the fluid, is within sulci at the right temporooccipital junction. And so, this would correspond to a sulcal effusion. It's still one location but because it's larger, so it's greater than 5 cm, but less than 10, we'd consider this moderate. If you had 2 areas or more than 1 area of ARIA-E, but it remains small, that would also be classified as moderate. And finally, if you look at the image on the right, you can see there's a large area of vasogenic edema in the right frontal lobe, as well as in the right parietal lobe. So, 2 large areas, both of which are greater than 10 cm. So, because of that, this would be classified as severe ARIA-E.

**Dr. Galvin:**

Right. And I guess what's really, I – what's, you know, could be challenging for clinicians and radiologists are not experienced with this, is, you know, on the left hemisphere there's also the more traditional kind of white matter or hyper-intensive signals that we see so often in older adults.

**Dr. Chiang:**

That's a – that's a very good point. And that's where I think, again, we need that baseline MRI to really figure out if this patient already has, you know, what we tend to call these is white matter hyperintensities related to microvascular change, or if this is – these are new white matter hyperintensities related to the timing of starting one of these therapies. So, that's absolutely a great point, we do see these white matter hyperintensities a lot. So, comparing with priors is important.

Similarly for ARIA-H, there is a grading scale to assess severity. So, in the first image you can see the circle around one area of superficial siderosis in the right temporal lobe. So, again, this is an area where there's hemosiderin within the sulci. And then the arrows are pointing to these punctate focal microhemorrhages, so these small foci of hemorrhage that are less than 1 cm and in the parenchyma. In this patient you can see there's one area of superficial siderosis and there are 2 foci of microhemorrhage. So, by the classification scheme, this is considered mild ARIA-H. In the middle image you can see the circle and the arrow pointing to 2 separate areas of superficial siderosis. So, with that, it's considered moderate ARIA-H. If this patient had more than 5 – between 5 to 9 microhemorrhages that would also qualify them as moderate ARIA-H, even without the superficial siderosis. And, on the image on the right, we can see the circle pointing out more than 10 – a clustered area of more than 10 microhemorrhages. So, by that definition they also would meet criteria for severe ARIA-H. If this patient had more than 2 areas of superficial siderosis, even without the microhemorrhages, they'd be considered severe ARIA-H.

**Dr. Galvin:**

So, you know, I think when we try to tie this all together, we're always trying to think about what – what – how we can apply this in clinical practice. So, I encourage the viewers to visit the American Society for Neuroradiology website to see what some of their recommended reporting templates are. Other quick tips, again, you can look for a directory of ARIA-experienced providers and this would be very helpful. So, again, resources that allow you to learn more about this and – and seek out colleagues who can assist you if you need that extra help. And as neurologists, we love differential diagnosis. So, Gloria, from your perspective what are we looking at from the radiologist's side? What are we thinking about when we see these changes?

**Dr. Chiang:**

Yeah. You know, I think as we mentioned, ARIA symptoms, they can mimic other neurological disease processes, so it's certainly not specific for ARIA. With certain symptoms you would think about acute ischemic stroke, for example. You'd think about subarachnoid hemorrhage, and you could think about PRES, posterior reversible encephalopathy syndrome.

**Dr. Galvin:**

Yeah. So, I think that is the challenge though, since these symptoms are not specific to ARIA. You know, someone walks in and, you know, they have a horrible headache, and they have dizziness, you know, these are the things that immediately pop into your head and a lot of these are older adults, so they might have hypertension and the like, so you'd have to think about PRES.

John, would you want to add anything to this? What else would you think about or is there any order where you would place these things in or is it based on what the patient is complaining about?

**Dr. Toledo:**

Yes. And so, here we have like several symptoms that you can have in these main conditions that we are considering for the differential diagnosis. What you can see with the different green check marks are those that are also present in ARIA. So, what you find is like acute onset hemiparesis or you see a facial paresis. Those are some specific visual field changes, those can be potentially more specific to a stroke syndrome presentation, or you see a brain stem presentation that would look very different from what you would see in ARIA. Two conditions where we can see some more overlap are the subarachnoid hemorrhage and PRES, and here, as we can see, the most frequent symptoms are going to be common to both. So, whereas mild ARIA-E presentation probably won't look clinically like subarachnoid hemorrhage, we would have more severe symptoms.

Something that is more challenging might be PRES because in –PRES we will have like a very similar clinical presentation, and in those cases, what will be helpful is to look back at the clinical history and the medications to find those risk factors for PRES that may help us differentiate these conditions.

**Dr. Galvin:**

So, let's dive look in a little bit more into the details. So, Gloria, take us through, you know, stroke, ARIA-E. What are we looking for? How's it different?

**Dr. Chiang:**

Yeah. I think in terms of ARIA-E, especially in the severe case you're going to see these large areas of T2 hyperintensity, these large parenchymal areas of T2 hyperintensity which can mimic what we see with large territory strokes as well. And so, this is an example where you can see this pretty large right hemispheric stroke with a lot of T2 hyperintensity. I think one thing that's very helpful for me in differentiating these two entities is, ARIA we think of as more of a vasogenic edema, so it should spare the cortex, versus strokes which usually involves both cortex and subcortical white matter. You can kind of see that signal going all the way to cortex. Another thing that's very useful is using the diffusion-weighted sequence, and so again, with vasogenic edema you don't have that restricted diffusion that you do with acute ischemia, and so, for example, even if it's bright on the diffusion-weighted imaging, you can see the ADC is also bright. So, this basically T2 shine-through related to vasogenic edema.

On the other hand, with acute stroke, you do have true restricted diffusion where you see bright signal on the DWI, but also ADC hypointensity. So, I think remembering those 2 things, cortex involvement and the diffusion-weighted imaging sequence can be very helpful in differentiation.

**Dr. Galvin:**

Does following, sort of, vascular distributions, is that helpful? Does ARIA-E cross vascular distributions or does it respect vascular distributions?

**Dr. Chiang:**

Yeah. I think in general vascular distributions can help as well. ARIA-E tends to be more patchy, so it may not be sort of confined to MCA territory, for example. So that would also be good though, I think, in terms of differentiating.

We've talked a little bit about PRES already and certainly the imaging can be very similar. So, both are more edema, so cortex is usually spared in both cases, and both tend to involve subcortical white matter, especially on the FLAIR sequence you can see these parenchymal areas of T2 hyperintensity. Classically PRES is involving the occipital lobes bilaterally so it's usually more symmetric,

whereas ARIA can be more patchy, more asymmetric, so that can be helpful. The other thing is again, sort of knowing the history. Did the patient come in with a lot of blood pressure fluctuations where you think about PRES? Are they on a medication that predisposes them to PRES versus ARIA-E?

**Dr. Galvin:**

Yeah. I was thinking that, you know, the fluctuations in blood pressure probably would be the one strongest clinical clue, right? So, those people who truly have uncontrolled hypertension are much probably statistically more likely to be affected with PRES than they are necessarily with ARIA, but you're right, I think it can be a real challenge.

And then to complete our conversation, Gloria, take us through how we sort of differentiate ARIA-E from subarachnoid hemorrhage.

**Dr. Chiang:**

Yeah. So, for subarachnoid hemorrhage, you'll often see high signal within the sulci. You can see in this right-sided image with the white circle, this sort of bright signal within the sulci which is due to blood in subarachnoid hemorrhage versus fluid or sulcal fusion in the ARIA-E case. So again, they can be very similar on the FLAIR sequence. In this case, you know, really the – the susceptibility-weighted, or gradient echo sequence could help you see the blood products in hemorrhage versus ARIA-E, because with ARIA-E it's – supposedly it's more of a fluid effusion and not blood products.

**Dr. Galvin:**

Great. And so, we talked about the things that they look like, but I think it's always, you know, what are those pitfalls – what are those interpretation challenges, you know, particularly at 3 o'clock in the morning when you're getting asked to look at some of these things, because that's when everybody shows up, you know, at the hospital is always at 3 o'clock in the morning, right? So, from an ARIA-E perspective, what are some of those pitfalls we need to look out for?

**Dr. Chiang:**

Yeah. So, here's some of the pitfalls that they've seen in a lot of the clinical trials for example. So, if you look at the left-sided image, you can see where it says ARIA-E. There's a circle that shows an area of T2 hyperintensity in the parenchyma which is compatible with sort of that vasogenic edema we see with ARIA-E, and what's nice is we have the follow-up after the patient stopped the medication and that actually went away. So that sort of corresponds to what we expect ARIA-E to do after – after stopping the medication. Whereas if you look at that same patient, the areas pointing to the small linear area of T2 hyperintensity, and certainly on that first image you would think maybe that's another area of ARIA-E just like the larger parenchymal area, it looks very similar, especially if it newly developed, you would think, okay, it's another site of ARIA-E, but interesting to note that on the follow-up after stopping the medication that persisted. So, in that case, that wasn't another site of ARIA-E, that was actually an incidental infarct, a small vessel infarct.

If you look at the middle image you know, these are some other instances in which you can be fooled into calling something ARIA-E. One thing we often talk about in terms of educating radiologists is as much as you can to try to keep these patients on the same type of scanner you know, the same 3.0 Tesla signal strength because different vendors can also have different technical parameters that could change the appearance. And so, in this case vender 1 you can see just some very subtle T2 hyperintensity just around the occipital horns, which is normal. But then it looks somewhat amplified on the vender 2 image. So, again, probably a technical difference and not true ARIA. With the hearing aids so, the hearing aid can give you a loss of signal on that side from the artifact, and then the adjacent slice can have this very bright signal. So, again, that can fool you into calling parenchymal edema or ARIA-E. And then something often very important in inpatients if they're on supplemental oxygen, you can actually get high signal within the sulci on a FLAIR sequence. So, we always try to remind our referring physicians and our techs to turn off the oxygen as much as possible so we don't get that artifactual signal within the sulci, which again, in this case, could fool you into calling a sulcal effusion in ARIA-E. So, just many things to keep in mind in terms of trying to stay consistent, as these patients are being monitored, and thinking of these other things that could affect the sequence.

**Dr. Galvin:**

Well, this makes me appreciate my radiology colleagues a lot more. When they ever hand me images, they're always nice images and I just get to look at them. I guess you hide all these bad images or difficulties from being displayed to the neurologist who ordered the scan.

**Dr. Chiang:**

Thanks, Jim.

**Dr. Galvin:**

Alright. So, we talked a lot about ARIA-E. Well let's now talk about ARIA-H, and what are some of those pitfalls or challenges that you'll face?

**Dr. Chiang:**

Yeah. So, similarly, many things to keep in mind in terms of pitfalls for ARIA-H. Microhemorrhages, as we've seen, they're these tiny little dots, often punctate dark dots and they can be very subtle sometimes. So, for example, this is one patient where it says motion and partial volume effects. The arrow is pointing to a very nice punctate focus of microhemorrhage in that first image. Well, in the second one, because the patient could be moving maybe the slice thickness is a little bit different, that microhemorrhage is actually blurred out. So, it could be a pitfall in terms of seeing or not seeing a microhemorrhage. Something to keep in mind. And, you know, with both grading echo and susceptibility-weighted imaging, you have susceptibility artifacts and effects, especially where there's bone involved, so skull base areas, frontal bones. You're going to have some of this dark signal that's sort of spilling into your parenchymal signal. So, something to keep in mind as well. And then finally, phase artifacts. So, especially when you've pulsation from adjacent veins that could give you sort of these wrap-around sort of artifacts that can fool you into calling ARIA. So, again, being aware of a lot of these artifacts is very important.

**Dr. Galvin:**

Alright. So, we talked about some of the pitfalls, we talked about what we're looking for, let's just review again and go over, well, what's recommended. What's the best way to image?

**Dr. Chiang:**

Yeah. So just to summarize what we've talked about so far, we've talked about how 3.0 Tesla MRI has greater sensitivity than 1.5 Tesla, so, if possible, to try to monitor all of your patients on a 3.0 Tesla scanner and to keep them consistently on the same type of scanner through their follow-up. Again, to have a slice thickness that's less than or equal to 5 mm, again, trying to keep that consistent to make sure you're not over or under calling ARIA.

Again, T2/FLAIR sequence is really the sequence you want to use. Conventional T2 is not going to let you see the sulcal effusions that you would see with ARIA-E. And SWI is definitely more sensitive than gradient echo, and so, it's advised if you have that, to use SWI. But, if you use gradient echo, again try to keep consistent.

**Dr. Galvin:**

Alright. That's great. So, this is optimal strategies. I want to throw out suboptimal, right? So, I want to throw out 2 situations and, you know, and again, so you can give your colleagues some thoughts about this. So, one, my claustrophobic patient is going to an open scanner. What can I see, what can't I see, what do I expect?

**Dr. Chiang:**

That's a tricky one because typically with open scanners, the image quality is not as good and so, they can do a FLAIR sequence, you will see the parenchymal edema, you probably will see the sulcal effusion. But in general, the scans I've seen that were done in open scanners, they usually don't have a great susceptibility-weighted sequence. So, it would mean that you would detect the ARIA-E, but you probably wouldn't detect the ARIA-H, and especially, microhemorrhages would be very limited on an open MRI. So, again, it would be working with neurology to see can we give the patient something to calm them down so they could get an appropriate MRI scan to follow them up.

**Dr. Galvin:**

Okay. Now the more difficult situation. Either a remoter situation where MRI is not available, or the patient has a contraindication to MRI, so metal an implantable device. What do you do?

**Dr. Chiang:**

That's another very tricky situation. So, you can get a CT scan. CT scan will show you the parenchymal edema, especially if it's moderate or severe, it's probably going to be large enough that you'll see that edema on CT. So, maybe you might be able to see ARIA-E. But, all the other findings of ARIA, such as the sulcal effusion, the microhemorrhage, the siderosis, you're not going to be able to see on CT. And so it's really going to be very limited in terms of monitoring these patients.

**Dr. Galvin:**

So, John, what do we do next?

**Dr. Toledo:**

We are going to now put all this together. So we had a patient who had just like a regular monitoring MRI or had some new onset symptoms that we thought were consistent with possible ARIA, and we got an MRI. So, here then we need to consider 2 things. One is, are there any clinical symptoms related to ARIA, and the other one is what are the imaging changes that we find. And so we're going to start from the righthand side of this slide where there are no symptoms, we were just monitoring at their pre-specified visits, and then there is only some mild changes on the MRI. Based on guidelines and experience of the trials, you can continue the treatment and what you will do is, you will change the frequency of the MRI scans, where you will check every month and – and see what is their progression, and then decide if you need to make any additional changes. Most of the patients in the clinical trials were able to restart later on the treatment, or continue the treatment. Then, it changes once we find moderate or severe changes on the MRI or patients are symptomatic. In those cases, we are going to suspend the treatment and we are going to continue also doing the monthly MRIs. Here Dr. Chiang discussed some differences between ARIA-E and ARIA-H. In ARIA-H, what we are looking at is stabilizations and no new events, so, basically, these findings are not going to disappear. However, when we are monitoring ARIA-E, the expectation is that there is going to be a resolution of the symptoms, and based on the experience on the different trials, approximately in – in 4 weeks a high 70%, low 80% of the patients have a resolution of ARIA-E. In those cases then, we can resume the treatment. Then, the question that there might be some guidelines or some expertise, and if you look at the label in – the ADA/FDA will be the cases that have mild symptoms and mild ARIA-E, and here there is no unified response. Where so basically the recommendations is based on clinical judgment. You can either suspend and monitor or continue the treatment and monitor monthly with MRIs watching for changes.

**Dr. Galvin:**

Alright. So again, I want to thank Dr. Chiang and Dr. Toledo for joining us in this really interesting interactive conversation. Thank you so much, Gloria.

**Dr. Chiang:**

Thank you. Thank you for this discussion.

**Dr. Galvin:**

Okay. And John, thank you.

**Dr. Toledo:**

Thank you for having me.

**Dr. Galvin:**

I want you to make sure you check out the closing module of this activity for multi-specialty discussion on the collaborative management of ARIA. This module is also summarized in a downloadable interactive infographic so you can access the information quickly on your own time. You can find the link on the program landing page.

Alright. Now you ruined my whole conversation. I don't know what I'm going to say. Okay.

**Announcer Close:**

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